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## THE CARBON DIOXID AND OXYGEN CONTENT OF STOMACH GAS IN NORMAL PERSONS

ARTHUR D DUNN, M D, AND WARREN THOMPSON, M D

OMAHA

The complaint of eructations of gas, or "gas on the stomach," is so common that any contribution to the knowledge of the chemistry and source of stomach gas should be of interest. The subject has been studied more or less intensively from time to time, but a review of the literature shows that more accurate methods must be employed in its investigation in normal as well as in abnormal persons before knowledge of much clinical value is obtained. Most of the literature appears under the caption of aerophagia, and has to do with the nervous origin and treatment of the unpleasant symptom of gas belching, but does not deal with the composition of the gas. Toward the end of the nineteenth century impetus was given to the more serious investigation of stomach gas by the discovery of inflammable gases in the stomach in certain cases of pyloric obstruction, and an extensive literature arose on this subject alone, since that time the view has prevailed that except for air swallowed in food or saliva, and by "air swallowers," the chief sources of stomach gas are fermentation and putrefaction.

Planer,<sup>1</sup> in 1860, was apparently the first carefully to investigate gas occurring in the stomachs of normal men and animals (Fleischfresser). He maintained that carbon dioxid occurred exceptionally in the stomach, was constantly present in the intestine and that it was a product of fermentation. Planer's views were based largely on the examination of the gaseous contents of stomach and intestines in dogs recently killed, and prevailed until Schierbeck<sup>2</sup> reopened the subject in 1892. Schierbeck first repeated Planer's experiments and examined the gas found in human bodies immediately after death. Segments of the gastro-intestinal tract were tied off and removed, the gas collected over mercury and analyzed. He found that the carbon dioxid content rose as the anus was approached. In the stomach, carbon dioxid values of from 12 to 20 per cent were obtained, and in the intestine values as

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1 Planer. Sitzungsberichte d Math-Natur Cl d K Akad d Wissensch, Wien, 1860, quoted by Schierbeck.

2 Schierbeck, N P. Ueber Kohlensaure im Ventrikel, Skand Arch f Physiol 3 437, 1892.

high as 50 per cent were commonly present. He found nitrogen, some oxygen and a trace of hydrogen in stomach gas, while in intestinal gas there was much hydrogen and little oxygen. In animals he excluded regurgitation from the intestine as a possible source of stomach gas by tying off the pylorus. In order to obtain estimates in the living, he filled the stomach with water at various stages of digestion, drew off the water mixed with stomach contents and estimated the carbon dioxide by driving it off through boiling into a standard baryta solution. This method permitted of the determination of the carbon dioxide content at all stages of digestion. Shierbeck found that the tension of carbon dioxide varied from 30 to 40 mm (3.9 to 5.3 per cent) before eating, to 130 mm (17.1 per cent) two hours after ingestion of food. Schierbeck concluded that there was a definite increase of carbon dioxide in the stomach during digestion. He believed carbon dioxide to be a constant product of the cell activity of the gastric mucosa, and to be an expression of the carbon dioxide tension in these cells and not a factor of the concentration of carbon dioxide in the stomach wall, because he found the percentage of carbon dioxide greater during digestion. Schierbeck inferred that sodium bicarbonate and hydrochloric acid might even be secreted synchronously from the mucous membrane and coming together liberate carbon dioxide. Hoppe-Seyler<sup>3</sup> analyzed gas from twenty-two pathologic cases under varying conditions of disease and diet, and found carbon dioxide tensions varying from 3.2 per cent in a case of post ulcer dilatation to 83 per cent in a case of carcinoma of the stomach, and oxygen values varying from none to 17.02 per cent in an "air swallower" without dilatation. Hoppe-Seyler stated that in doubtful cases an analysis should determine whether the gas is swallowed or comes from fermentation, indicating the clinical application of gas analysis to stomach disorders. He concluded that the carbon dioxide content was greater when free hydrochloric acid was absent (a conclusion exactly opposite to the one arrived at by Shierbeck), that frequently stomach gas consisted of air which had been swallowed, from which a portion of oxygen has been taken and carbon dioxide added, and that gas might find its way into the stomach from the duodenum. He attributed the origin of stomach gas largely to bacterial action, a view which figures widely in present day clinical beliefs. In 1912, Woodyatt and Graham<sup>4</sup> outlined clearly the problems involved in the subject of stomach gases, and studied three cases of acute dilatation of the stomach. In a case in which they gave the results of their analyses, no inflammable gas was found, 24 per cent carbon dioxide,

<sup>3</sup> Hoppe-Seyler, G. *Deutsch Arch f klin Med* **50** 82, 1892

<sup>4</sup> Woodyatt, R. T., and Graham, E. A. *Alimentary Respiration*, *Tr Chicago Path Soc* **8** 353, 1912

4 per cent oxygen and 72 per cent nitrogen, fluid aspirated from the stomach produced no gas on incubation at 37 C. Woodyatt and Graham advanced the theory that in acute dilatation of the stomach there was a lack of available oxygen in the tissues with edema, hemorrhagic or serous exudation into the stomach, and impaired muscular tone, they concluded that "the distension of the stomach is a consequence of the gas evolution in a stomach whose wall is already crippled, atonic and unable to expel gas. The gas comes at least in part from the stomach wall, either directly or as a result of the action of the gastric juice on the carbonates of the exudate." Room air was introduced by them into the normal stomach, withdrawn in five minutes for analysis. They were convinced that the gastric mucosa had the power of liberating carbon dioxide.

Kantor,<sup>5</sup> in 1918, gave an extensive review of the literature and performed a few preliminary gas estimations on an unselected series of persons, aspirated at various intervals after eating. The average of five analyses gave carbon dioxide, 41 per cent, oxygen, 17.2 per cent, nitrogen, 79 per cent. The carbon dioxide values varied from 2 to 62 per cent.

It is apparent from the literature that carbon dioxide is the one gas constantly present in the stomach, and that carbon dioxide usually occurs in excess of the amount found in atmospheric air. Therefore, it was thought that a quantitative study of the carbon dioxide content of stomach gas in normal persons, under varying conditions, might throw some light on the origin of this gas, a subject in regard to which there seemed to be no unanimity of opinion, and also be of value as a preliminary to the quantitative study of stomach gas in disease. Obviously, there can be but three possible sources for this excess of carbon dioxide, viz: (1) Secretion or diffusion of carbon dioxide from the stomach wall, (2) production of carbon dioxide from the food contents by bacterial fermentation, (3) regurgitation of duodenal contents into the stomach, which seems an unlikely source, as Schierbeck found the same carbon dioxide values, whether the pylorus was occluded or open. We decided, after a few preliminary analyses in patients complaining of "gas on the stomach," to confine our observations for the present to normals, as we had no basis for the estimation of abnormal variations, and to approach the problem in the following manner: first, to make careful quantitative determination of the carbon dioxide and oxygen content of gas obtained from the fasting stomach, second, to determine the changes occurring in the carbon dioxide and oxygen content in atmospheric air introduced into the fasting stomach,

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<sup>5</sup> Kantor, J. L. A Study of the Atmospheric Air in the Upper Digestive Tract, *Am J M Sc* **155** 829, 1918.



third, to ascertain whether appreciable differences occurred in atmospheric air introduced into the stomachs of the same individuals, both when fasting and after a full meal, and finally, to ascertain whether gas was formed by incubation of stomach contents, and if so, under what conditions

In order to learn to what extent carbon dioxide was present in the fasting stomach, the following method was used. To a T tube were attached a duodenal tube, a sampling tube and a Luer syringe filled with tap water. The air in the system was displaced as far as possible by water from the syringe, the syringe left attached, and the duodenal tube swallowed. When the duodenal bucket reached the stomach, the water was aspirated from the system by the syringe, the rubber attachment to this arm was clamped with a pinch cock, and the gas collected over mercury in a sampling tube. Analyses of four samples thus obtained from fasting stomachs were made with a standard Haldane gas apparatus and gave the following results

TABLE 1—ANALYSIS OF SAMPLES OBTAINED AT 8 A. M. FROM FASTING STOMACH

Number	Carbon Dioxid	Oxygen	Nitrogen (by difference)
1	7.26	16.30	76.44
2	4.67	15.10	80.23
3	8.68	15.93	75.39
4	6.63	16.40	76.79

It was found that satisfactory samples of gas could be obtained in only two out of nine persons on whom the attempt was made. Fluoroscopic study of the fasting, as well as of the food containing stomach, showed that gas bubbles of sufficient size to furnish 50 c.c. of gas were the exception rather than the rule. Rough estimates made from fifty unselected roentgenograms gave the average size of the bubble as approximately 50 c.c. Even though sufficiently large, the gas bubble was often so placed that the duodenal bucket, because of its tendency to follow the gutter of the lesser curvature, could not be made to tap it, furthermore, in the majority of persons examined with the fluoroscope in the sitting or standing position, the gas bubble was found to be at a higher level than the cardiac inlet. The introduction of a fixed quantity of atmospheric air into the stomach would obviate difficulties in sampling. Besides, there is usually a certain amount of air in the stomach which has been swallowed with the food or saliva. Therefore, atmospheric air must, as a rule, enter into any gas mixture found in the stomach, and the introduction of a given amount of room air into the fasting stomach would merely supply the normal gas body, minus food and saliva. In the case of the fasting stomach, analyses of samples of gas taken at varying intervals after the introduction of atmospheric air

into the stomach would show whether carbon dioxid was secreted into the stomach, and if so, to what degree and at what rate. The method used was as follows. A duodenal tube was introduced into the stomach and 300 c c of air was injected into the stomach, the patient instructed to avoid belching or swallowing as much as possible, the tube clamped and left in situ, and samples taken at varying intervals. The analysis of ten samples, taken from twenty to thirty minutes after the introduction of 300 c c of room air into the stomach gave carbon dioxid, 5.26 per cent, oxygen, 17 per cent. The results of two additional experiments on successive days in the same subject, with sampling at fixed intervals are shown in Table 2. It is noteworthy that in the same individual on successive days, under exactly similar conditions, an average variation of more than 1 per cent occurred in the carbon dioxid and 0.5 per cent in oxygen. Inasmuch as the main body of stomach gas following the ingestion of food is obviously swallowed atmospheric air, the determination of the changes that might occur in air injected into the fasting stomach was particularly pertinent in an effort to determine the normal gas content and its sources.

TABLE 2—CHANGES THAT MIGHT OCCUR WHEN AIR IS INJECTED INTO THE FASTING STOMACH

Experi- ment	Room Air Injected	10 Minutes		20 Minutes		35 Minutes		50 Minutes		Average	
		Carbon Dioxid	Oxy- gen	Carbon Dioxid	Oxy- gen	Carbon Dioxid	Oxy- gen	Carbon Dioxid	Oxy- gen	Carbon Dioxid	Oxy- gen
No. 1	300 c c	1.8	19.3	8.1	16.9	5.9	17.5	4.1	17.1	4.98	17.7
No. 2	300 c c	0.2	21.6	2.9	18.0	6.3	16.7	6.4	16.5	3.95	18.2

Time denotes the interval between the introduction of room air into the fasting stomach and the taking of the sample.

In order to ascertain what influence the presence of food might have upon the relative gas values at stated intervals, 300 c c of room air were injected into the stomach of normal persons at varying periods of time after an ordinary breakfast. Controlled analyses of samples from the same persons while fasting were also made. The results of this series of experiments are given in Table 3. It is apparent from a study of Table 3 that the rate and degree of liberation of carbon dioxid does not depend on the presence of food in the stomach in normals. In Experiment 1 the average amount of carbon dioxid obtained was practically the same in the fasting and in the full stomach, in Experiment 2 the average amount of carbon dioxid was 0.92 per cent greater in the fasting stomach, in Experiment 3, 0.90 per cent greater in the digesting stomach, in Experiment 4 the average was 6 per cent carbon dioxid in the fasting stomach and 4.8 per cent after food. This is at variance with Schierbeck's observations, who found that the carbon dioxid tension paralleled the acidity. His carbon dioxid estimates were

made by driving the carbon dioxide by boiling from stomach contents which were obtained by washing with water. Boiling acidulated stomach contents releases the carbon dioxide from the food carbonates, and would account for the greater carbon dioxide values that he found in the presence of hydrochloric acid. An Ewald test breakfast acidulated to a normal free hydrochloric acid content will liberate from four to five volume per cent carbon dioxide. The same carbon dioxide values obtain whether the test breakfast is acidulated in the stomach by its secretion or in vitro with hydrochloric acid. That hydrochloric acid in stomach contents inhibits the production of carbon dioxide is amply borne out by fermentation experiments.

TABLE 3 — INFLUENCE OF THE PRESENCE OF FOOD ON RELATIVE GAS VALUES

Exptl	300 C c Room Air Injected	10 Min		20 Min		35 Min		50 Min		65 Min		Average		Remarks
		CO <sub>2</sub>	O <sub>2</sub>	CO <sub>2</sub>	O <sub>2</sub>	CO <sub>2</sub>	O <sub>2</sub>	CO <sub>2</sub>	O <sub>2</sub>	CO <sub>2</sub>	O <sub>2</sub>	CO <sub>2</sub>	O <sub>2</sub>	
1	Fasting	55	193	58	184	61	179	57	174	46	147	554	1754	Stomach secretion with saliva, T A 15, HCl 6
	1½ hours after full breakfast	41	197	61	181	71	169	68	168	32	181	546	1792	Stomach contents well digested, T A 30, HCl 15
2	Fasting	27	200	43	195	44	177	52	165	54	182	442	1838	Mucus and saliva, no free HCl
	2 hours after full breakfast	14	192	19	168	40	180	49	165	53	169	350	1748	Contents, T A 20, free HCl 0
3	Fasting	40	199	49	189	56	183	65	186	71	166	562	1846	Mucus and saliva, T A 16, free HCl 5
	1½ hours after full breakfast	57	192	62	168	67	179	67	157	73	164	652	172	Well digested stomach contents T A 37, free HCl 14
4	Fasting	36	196	48	184	76	174	68	169	72	173	60	1792	1 glass of water 1 hr before, 50 c c stomach contents, T A 34, HCl 20
	1 hour after full breakfast	17	193	81	169	59	175	41	171	45	190	486	1796	Contents well digested, T A 34, free HCl 20

Time designated is number of minutes after introduction of room air into the stomach at which the sample was taken.

Analyses of room air varied CO<sub>2</sub> from 0.9 to 0.23 per cent and O<sub>2</sub> from 20 to 20.97 per cent, depending on whether the windows were open or closed, the number of people about, and the number of flames burning in the laboratory.

In order to determine the possibility of fermentation as a source of stomach gas, stomach contents, obtained after the usual Ewald test breakfast from one hundred unselected cases, were incubated at 37 C for twenty-four hours in saccharimeters. In only thirty-one instances was there any evidence of gas formation as shown either by a large or a few minute bubbles. In seventeen cases only was there a bubble of sufficient size to estimate. In all cases, except three, in which there was any evidence of gas production, there was no free hydrochloric acid present. In the three cases that showed gas in the presence of free hydrochloric acid the total acidity was below 20. All stomach contents without free hydrochloric acid, except four, showed evidence of

fermentation The presence of free hydrochloric acid in quantity in the stomach contents practically precludes the production of carbon dioxide by fermentation It is obvious from these experiments, as well as from the absence of marked difference in the carbon dioxide content in air introduced into the fasting and digesting stomach, that fermentation can have little to do with the carbon dioxide content in the stomach gas of normal persons

#### COMMENT

These experiments show that within an hour after the injection of room air into a normal stomach, the carbon dioxide reaches a tension equivalent to from 4 to 9 per cent The carbon dioxide values lie mostly between the pressure at which carbon dioxide is held in arterial blood and alveolar air (5.5 per cent carbon dioxide), and in the tissues (from 7 to 9 per cent carbon dioxide) <sup>6</sup> In only one instance in a normal fasting stomach was a carbon dioxide value obtained (10 per cent) higher than that given for venous blood A constant reduction of the oxygen content was noted, but the removal of oxygen from the injected air was much less rapid than the passage of carbon dioxide into it The oxygen content in no instance fell sufficiently to approximate that of alveolar air (14 per cent) within one hour's time, and in no instance have we found oxygen values as low as those prevailing in arterial blood (from 12 to 13 per cent) We must conclude, therefore, that when atmospheric air is introduced into the stomach it tends to come into equilibrium as far as its carbon dioxide and oxygen content is concerned with the blood gases of the stomach wall, rapidly in the case of the carbon dioxide, slowly in the case of the oxygen This corroborates, in part, the experiments of Ylppo,<sup>7</sup> carried out on himself, in which he found that atmospheric air, as such, disappeared from the stomach in from forty to sixty minutes, that the residue had a rather constant oxygen-carbon dioxide ratio, which approximated that of blood gases Simultaneous alveolar air analyses showed that there was a constant ratio between stomach and blood gases In our experiments, however, values much higher than those of alveolar air were commonly obtained Of interest in this connection are the experiments of Haggard and Henderson,<sup>8</sup> who injected air into the abdominal cavity and found that within one hour it came to have a carbon dioxide tension equivalent to that of arterial blood and alveolar air

It is obvious that gaseous interchange in the stomach is a fundamental physiologic process governed by fixed laws It is not unlikely

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6 Howell, W. H. *A Text Book of Physiology* Philadelphia: W. B. Saunders Company, 1918, p. 689

7 Ylppo, A. *München med. Wchnschr.* **63** 1650, 1916

8 Haggard, H. W., and Henderson, Y. *J. Biol. Chem.* **38** 71, 1919

that measurable differences in rates and degrees of diffusion may occur in pathologic processes such as cardiac decompensation (asphyxia), arteriosclerosis, ulcer, carcinoma, dilatation of the stomach, hyperthyroidism, aerophagia, etc., and that the study of the variations in gaseous interchange occurring in the stomach in both general and in gastrointestinal disease may lead to knowledge of clinical value. For example, it has long been assumed that belching is a pastime for the neurotic, an evil habit of which he must be broken by "psychical" measures. It has been spoken of as an "obsessing tic," and a "neuropathic predisposition" postulated. A study of the whole subject of aerophagia in the light of accurate gas analyses may reveal a cause of more compelling therapeutic interest for this unpleasant symptom complex than that which allows it to be viewed in the yellow light of "neurotic perversity." The question of "why do people with stomach trouble belch gas" has never been answered completely.

#### CONCLUSIONS

- 1 Atmospheric air introduced into the stomach tends to come into equilibrium with the blood gases within one hour in the case of carbon dioxide, and considerably later, if at all, in the case of oxygen.

- 2 All the carbon dioxide found in the stomach gas of normal persons, whether fasting or after a full meal, can be accounted for by secretion or diffusion from the gastric mucosa.

- 3 In the study of stomach gas occurring in pathologic conditions, an upper normal limit of at least 9 per cent carbon dioxide tension must be postulated.

# STUDIES IN THE CHEMOTHERAPY OF BACTERIAL INFECTIONS

## II THE CHEMOTHERAPY OF EXPERIMENTAL LOCALIZED BACTERIAL INFECTIONS WITH SPECIAL REFERENCE TO PLEURITIS<sup>1</sup>

JOHN A KOLMER, M D

PHILADELPHIA

In serum and chemotherapeutic investigations in bacterial infections, animals are usually infected by subcutaneous or intraperitoneal injections of the test microorganism resulting in the production of generalized infections associated with bacteremia and terminating fatally in a few days, or in a few weeks, as in experimental tuberculosis. As a general rule, the test animals are very susceptible to the test micro-parasite, and the results are evaluated by the duration of the lives of treated animals as compared with infected but untreated controls.

In experimental serum therapy of such bacterial infections as are produced by virulent pneumococci, streptococci, meningococci, anthrax bacilli, and so forth, this method is generally satisfactory because owing to the low toxicity of the immune serums for the test animals, relatively large amounts may be given to influence favorably an otherwise rapidly fatal bacteremia and septicemia. But in chemotherapeutic studies in bacterial infections the *dosis curativa* of a medicament is likely to be but slightly less than the *dosis tolerata* or the *dosis lethalis*, and rapidly fatal and generalized infections do not disclose possible, although feeble, curative effects on the part of the compound under study, and thereby fail to yield information of value for the conduct of chemotherapeutic investigations.

For example, the maximum tolerated dose of ethylhydrocuprein hydrochlorid (optochin) for mice, by intravenous and intraperitoneal injection, is approximately from 20 to 40 mg per kilo of body weight. When these animals are infected with 50 minimum lethal doses of Type I pneumococci, Cohen, Heist and myself<sup>1</sup> found that at least 20 mg of drug per kilo must be administered at about the same time as the cocci to prolong the lives of approximately 20 per cent of animals for an indefinite period. This amount was one half or more the highest

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\* From the Dermatological Research Institute of Philadelphia and the Pathological Laboratories of the Graduate School of Medicine of the University of Pennsylvania.

<sup>1</sup> Cohen, S S, Kolmer, J A, and Heist, G D. The Protective and Curative Value of Quinin and Urea Hydrochlorid, Ethylhydrocuprein and Other Cinchona Derivatives in Experimental Pneumococcus Infections, *J Infect Dis* 20 313, 1917.

tolerated dose and indicates the very small margin between *dosis tolerata* and *dosis curativa* of ethylhydrocuprein hydrochlorid for mice with pneumococcus bacteremia. Moore<sup>2</sup> has observed somewhat better results than we in the treatment of pneumococcus bacteremia of mice with the ethylhydrocuprein base, but the margin between the toxic and curative doses was likewise small.

Much better results, however, have been observed by Sands and myself<sup>3</sup> in the treatment of pneumococcus pleuritis of guinea-pigs. We have been able to produce well defined lesions by injecting intrapleurally 0.5 cc of twenty-four hour dextrose blood broth cultures of pneumococci of moderate virulence into the right pleural sac, as a general rule, this was followed by the development of acute suppurative pleuritis on both sides with pericarditis. The lesions, however, were not strictly confined to the pleurae since both lungs frequently showed inflammatory changes and pneumococci were generally found in the blood. Extremely virulent cultures were unsatisfactory inasmuch as rapidly fatal bacteremias ensued, cultures of moderate virulence in broth, rather than suspensions in saline solution, produced the best results, the broth probably aiding in the production of suppurative changes.

For guinea-pigs the maximum tolerated dose of ethylhydrocuprein hydrochlorid by intrapleural injection is approximately from 20 to 30 mg per kilo, being the same or slightly less than the maximum tolerated dose by intravenous injection.<sup>4</sup> The injection of 0.5 cc of 1:500 solution into each pleural sac of guinea-pigs weighing 400 gm within twenty-four hours after the injection of pneumococci, usually cured the pleuritis and prolonged the lives of the animals for indefinite periods.<sup>5</sup> The total amount injected was, therefore, 1 cc of 1:500 per 400 gm, corresponding to 10 mg per kilo and equivalent to one third the maximum tolerated dose. These experiments have indicated that to study the results of treatment of these more or less localized pneumococcus lesions in animals possessing some natural immunity,

2 Moore, H. F. The action of Ethylhydrocuprein (Optochin) on Type Strains of Pneumococci in Vitro and in Vivo, and on Some Other Microorganisms in Vitro. *J. Exper. M.* **22** 269, 1915.

3 Kolmer, J. A., and Sands, J. R. Chemotherapeutic Studies with Ethylhydrocuprein Hydrochlorid in Experimental Pneumococcus Pleuritis, *J. Exper. M.* **33** 693, 1921.

4 Kolmer, J. A. Route of Administration of Drugs in Relation to Toxicity in Chemotherapeutic Investigations, *J. Pharmacol. & Exper. Therap.* **17** 431, 1921.

5 The protective and curative effects of ethylhydrocuprein hydrochlorid were improved by the addition of sodium oleate and boric acid (Lamar).<sup>6</sup>

6 Lamar, R. V. Action on the Pneumococcus and Its Experimental Infections of Combined Sodium Oleate and Antipneumococcus Serum, *J. Exper. M.* **13** 1, 380, 1911, *ibid.* **14** 256, 1911, *ibid.* **16** 581, 1912.

they are better for bringing out the curative effects of a drug than is possible in experiments employing highly susceptible animals with rapidly fatal bacteremias

Experiments *in vitro* have shown that mixtures of equal parts of pleural pus containing very large numbers of virulent Type I pneumococci and 1 1000 solutions of ethylhydriocuprein hydrochlorid giving a final dilution of 1 2000 result in the complete destruction of all pneumococci in approximately thirty minutes at body temperature. This corresponds to 10 mg of the drug dissolved in 10 c c of pus. If the pus in both pleural sacs of guinea-pigs weighing approximately 400 gm amounted to 10 c c, the injection of 2 c c of 1 500 solution of drug (1 c c into each sac) would give a final dilution of approximately 1 1000. This dose is equivalent to 10 mg per kilo and even if all the drug were absorbed, it would be at least one third of the maximum tolerated dose.

In other words, it would appear that in experimental pneumococcus pleuritis sufficient ethylhydriocuprein hydrochlorid may be injected into the pleural sacs to render the contents decidedly pneumococcidal without toxic effects, whereas the same amounts injected into the blood are without effect on the local lesions or pneumococcus bacteremia.

Similar results have been observed by Idzumi and myself<sup>7</sup> in the treatment of experimental pneumococcus meningitis of rabbits with ethylhydriocuprein hydrochlorid.

By subthecal injection the maximum tolerated dose is approximately 0.5 c c of a 1 500 dilution per kilo of body weight, being equivalent to 1 mg per kilo. By this route of administration the drug is twenty or more times more toxic than by intravenous injection.

Experiments *in vitro* with purulent spinal fluids containing virulent Type I pneumococci, have shown that the drug is germicidal in final dilutions of 1 2000 in thirty minutes, 1 4000 in one hour, and 1 10,000 in one and a half hours at body temperature.

The subthecal injection of rabbits with 0.5 c c of a 1 1000 dilution per kilo within from four to six hours after the subthecal injection of pneumococci of moderate virulence, results in saving a large percentage of animals against an otherwise fatal suppurative meningitis and bacteremia. This dose corresponds to 0.5 mg per kilo and is at least one half the maximum tolerated dose by subthecal injection.

Assuming that there are from 2 to 3 c c of spinal fluid per kilo of body weight, the final dilution of drug in the subarachnoid space

7 Kolmer, J. A., and Idzumi, G. Chemotherapeutic Studies with Ethylhydriocuprein and Mercurophen in Experimental Pneumococcus Meningitis in Rabbits, *J. Infect. Dis.* **26** 355, 1920.



was approximately 1 6000, providing diffusion was complete, according to the results of the bactericidal tests in vitro, this dilution should possess pneumococcal activity

The intravenous injection of rabbits with 10 mg of ethylhydrocuprein per kilo (equivalent to one half the maximum tolerated dose) had no influence on the course of pneumococcus meningitis, in fact, the animals succumbed somewhat more rapidly owing to lowered resistance due to the infection. But, as stated above, the subthecal injection of 0.5 mg per kilo (equivalent to one half the maximum tolerated dose by this route) was frequently followed by beneficial results

In my opinion, the treatment of experimentally infected serous cavities and especially the pleural cavities, constitutes a procedure of distinct value in chemotherapeutic studies in bacterial infections when the curative dose of a compound is likely to be but slightly less than the maximum tolerated dose. In serum therapy or in chemotherapy with such arsenical compounds as arsphenamin in spirochetic or trypanosome (*Trypanosoma*) infections, when the curative amount is many times less than the toxic amount, generalized infections are suitable, since the compound may be given in relatively large doses without danger of poisoning

Studies in the production of experimental tuberculous pleuritis by Ogawa and myself,<sup>8</sup> have shown that it is possible to produce a tuberculous infection limited to the pleurae and lungs with such extension of the disease to the pericardium and lymph glands as occurs by direct lymphatic absorption and continuity of tissues. The intrapleural injection of guinea-pigs with bovine tubercle bacilli is followed by metastases to the spleen, liver and other organs, that is, a generalized infection follows. Human tubercle bacilli likewise produce generalized infections but in not as high a percentage of animals. Human tubercle bacilli injected into the pleural cavities of adult rabbits generally (but not always) resulted in localized lesions, bovine bacilli regularly produced generalized lesions in these animals. Bovine and human tubercle bacilli injected into the pleural cavities of adult white rats and adult dogs have resulted in the production of localized lesions. By suspending the bacilli in broth instead of saline solution, the local suppurative changes generally have been increased. While extensive chemotherapeutic studies have not been made with these lesions, I believe that localized tuberculous pleuritis and pneumonitis offer more favorable lesions for studies in vivo than generalized and widespread lesions, the medications being injected into one or both pleural cavities at varying intervals after the injection of the bacilli into the right sac

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<sup>8</sup> Kolmer, J. A., and Ogawa, I. Experimental Tuberculous Pleuritis as an Aid to Chemotherapeutic Investigations in Tuberculosis, *Am Rev Tuberc* 6: 437, 1921

In this connection the experiments of Gay and Stone<sup>9</sup> in the production of experimental pleuritis in rabbits are of interest. These investigators have studied the effects of vaccine and serum therapy on these lesions, and later Gay and Morrison<sup>10</sup> experimented with various dyes injected into the infected cavities, but with negative results.

For the production of localized bacterial infections of serous cavities for purposes of chemotherapeutic research it would appear necessary to select test animals possessing some natural immunity for the test bacterium, furthermore, the bacterium should be of moderate rather than of extreme virulence. These factors decrease the chances of producing generalized infections and bacteremias and favor the development of localized lesions spreading only by direct continuity of tissues. Under these conditions subtoxic amounts of medicament injected into the cavities may produce therapeutic results even when diluted with inflammatory exudates and thereby yield information of value in chemotherapeutic investigations.

#### SUMMARY

1 Studies with ethylhydrocuprein hydrochlorid (optochin) in the treatment of experimental pneumococcus pleuritis and meningitis have indicated that in chemotherapeutic investigations in bacterial infections, localized infections of serous cavities offer a more favorable means for eliciting therapeutic effects of a medicament than generalized infections and bacteremias.

2 In localized infections of serous cavities it is possible to inject into the sacs sufficient amounts of medicament to render the contents bactericidal and curative. These amounts may be at least one half the maximum tolerated doses. In rapidly fatal generalized infections with bacteremias, however, the intravenous injection of one half the maximum tolerated dose may be without therapeutic effects.

3 Localized bacterial infections of serous cavities would appear to be especially useful for chemotherapeutic studies with medicaments possessing high toxicity when the margin between *dosis tolerata* and *dosis curativa* is small.

4 In the production of localized infections of such serous cavities as the subarachnoid space, pleural sacs and pericardium, test animals possessing some natural immunity to the test bacterium should be

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9 Gay, F. P., and Stone, R. L. Experimental Streptococcus Empyema Attempts at Prevention and Therapy by Means of Vaccines and Serum, *J. Infect. Dis.* 26: 265, 1920.

10 Gay, F. P., and Morrison, L. F. Experimental Streptococcus Empyema Attempts at Dye Therapy, *J. Infect. Dis.* 28: 1, 1921.

chosen, like the guinea-pig for pneumococcus pleuritis and pericarditis, the cat or dog for pneumococcus meningitis and the dog or rat for tuberculous pleuritis. The test microorganism should be of moderate rather than extreme virulence, in order to reduce the invasiveness or aggressiveness of the bacteria for the blood and other organs.

# AN EXPERIMENTAL AND CLINICAL STUDY OF QUINIDIN SULPHATE I EXPERIMENTAL<sup>†</sup>

HORACE MARSHALL KORNS, M.D.

CLEVELAND

Experiments were devised for the purpose of studying some of the effects of quinidin on the normal dog and guinea-pig heart. The method employed was comparatively simple. Dogs were fully anesthetized with ether, except in one instance when anesthesia was secured by means of chlorbutanol and morphin. The right fore leg and left hind leg were shaved, and suitable electrodes applied and connected to the string galvanometer in the usual way. All experimental electrocardiograms were therefore derived from Lead II. The thorax was not opened in any case, no direct auricular contacts were employed, and all observations were conducted on the spontaneously beating heart. When observations on the vagi were desired these nerves were isolated for a considerable distance in the neck, sectioned, and the peripheral end stimulated from the secondary coil of the ordinary inductum. A signal in circuit with the primary coil marked the beginning and end of stimulation. Quinidin sulphate supplied by Merck, the same preparation which was used in the wards, was dissolved in physiologic solution of sodium chloride and injected in measured amounts from a buret into the femoral vein. Atropin, which was used in one animal, was injected subcutaneously.

Anesthesia was secured in guinea-pigs by means of ether in conjunction with methane or paraldehyd. The electrocardiogram was recorded from an axial lead, comparable to the conventional Lead II, derived in some instances from metal electrodes, one inserted beneath the skin of the neck, the other thrust into the rectum. Where polarization became appreciable, the metal contacts were supplanted by non-polarizable boot electrodes inserted beneath the skin of the neck and left hind leg. Quinidin sulphate, dissolved in distilled water by the addition of a few drops of concentrated sulphuric acid, was given to these animals by stomach tube in one massive dose of 0.67 gm. No observations on the vagi were attempted. In all other respects the procedure was the same as for the dogs.

In each animal a complete series of control records was made. When vagus effects were to be studied, the tonic activity of both nerves was established, and the minimal effective stimulus determined. An accurate time record of all electrocardiograms and experimental pro-

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<sup>†</sup> From the Medical Clinic of Lakeside Hospital and Western Reserve University.

cedures was kept. In dogs the immediate effect of each intravenous injection was thoroughly studied in records which began with the injection and were continued at frequent intervals, and the remote effects of the total dosage were observed throughout each experiment until the animal died from quinidin poisoning. In guinea-pigs the steadily progressing changes in the electrocardiogram were photographed at frequent intervals over a period of sixty to ninety minutes, at the end of which time death usually occurred.

Instead of reproducing detailed protocols of the experiments, I shall summarize the more important facts which have been established in analysis and measurement of approximately 1,000 feet of records.

*Rate of Impulse Discharge from the Pacemaker*—The inevitable result in all experiments is ultimate retardation of the rate of beating, but temporary increases are frequently seen immediately after single injections of the drug. Lewis and his associates<sup>1</sup> have shown that retardation is due to a direct action on the Purkinje structures of the pacemaker, for it is independent of the action of atropin. This may also be inferred from our experiments, for it occurs in spite of the contrary effect which is to be expected from paresis of the vagi by quinidin. Temporary increase in rate of beating after single injections is to be explained either as the result of a predominant effect on the vagi, or delay of the effect on the structures of the pacemaker. The latter seems much the more probable. Quinidin retards the rate at which impulses are discharged from the pacemaker whether the latter be situated in the *S-A* node or the *A-V* node, a fact well illustrated in the case of Dog 1. Immediately after the first injection of the drug, and coincidentally with the development of a high grade of intra-auricular block, the function of pacemaker was assumed by the *A-V* node, but the rate of beating was progressively slowed notwithstanding. These results are in accord with those obtained by Schott,<sup>2</sup> Boden and Neukirch<sup>3</sup> and Lewis, et al.<sup>1</sup> Cohn and Levy<sup>4</sup> saw no constant effect on rate of beating in their dogs.

*Intra-Auricular Conduction*—Lewis and his associates have shown that quinidin greatly slows conduction in the auricle when the heart is driven at a constant rate of about 200 per minute. This disturbance in conduction proceeds to "intra-auricular block," which is characterized by gross irregularity of the auricular curves. This phenomenon of intra-auricular block appears in electrocardiograms of hearts beating in response to their own rhythm in the earlier paper of Boden and Neukirch, but was evidently misinterpreted by these authors. So far

1 Lewis, Drury, Iliescu and Wedd. *Heart* **9** 55, 1921.

2 Schott. *Deutsch Arch f klin Med* **134** 208, 1920.

3 Boden and Neukirch. *Deutsch Arch f klin Med* **136** 181, 1921.

4 Cohn and Levy. *Proc Soc Exper Biol & Med* **18** 283, 1921.

as I am aware, it has not been described in the spontaneously beating heart. It is evident that intra-auricular block which is responsible for irregularity of the auricular curves when the heart is driven at a constant rate will be represented in the heart which beats in response to its own impulses by regular, but arrhythmic, auricular waves. I have noted this occurrence in a patient shortly after the resumption of normal mechanism, and have frequently produced the condition in experiment. In the spontaneously beating heart intra-auricular block is essentially a condition in which the auricles and ventricles beat independently of each other, at nearly the same rates, or at widely different rates. The auricle responds to the *S-A* node the ventricle to the *A-V* node. In the early stage of development the auricular rate slows, but remains rhythmic; later, the auricular systoles become grossly arrhythmic. Assumption by the *A-V* node of the function of pacemaker for the ventricle is probably due both to actual starvation of its natural quota of transmitted impulses, and to irregularity of the auricular inter-systolic intervals. The fact that the *A-V* node always assumes this function, at least in the earlier stages of poisoning, is proof that it is not functionally depressed to the same extent as the auricular muscle, although, as has been noted above, its rate of discharge of impulses is progressively retarded as poisoning increases. One might justly infer that if for any reason the *A-V* node were unable to assume pacemaker function following intra-auricular block, the resulting condition would closely approximate what is commonly known as "sino-auricular block." In other words, it is suggested that so-called "sino-auricular block" may really be intra-auricular block unaccompanied by *A-V* nodal escape. One would then expect *S-A* block to consort with intra-auricular block at a comparatively late stage of poisoning, which is precisely what occurs (Figs. 5 and 15). Bearing in mind the established relation of the vagus to *S-A* block it is significant that the block occurs after a large part of the parietic action of quinidin on the vagus has been exerted. As Lewis and his associates<sup>5</sup> have suggested, and as one may infer from the paper of Boden and Neukirch, intra-auricular block is usually partial, but may be complete, resulting in auricular asystole (Fig. 10).

Electrocardiograms of intra-auricular block are likely to be confused with those of *A-V* rhythm, but a careful analysis of the curves clearly defines the condition in a manner presently to be explained. It is at this point that Boden and Neukirch were misled. The hypothesis of *A-V* rhythm is inconsistent with our conception of intra-auricular block, for in the former it is clear that the whole heart is responding to impulses from but one center, whereas in the latter, two separate

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5 Lewis, Drury and Iliescu. Heart 9 21, 1921

centers control auricles and ventricles. It is, therefore, impossible to conceive that the two entities might coexist. Development of the conception of intra-auricular block improves our sense of criticism in regard to certain cases which might otherwise be interpreted unreservedly as *A-V* rhythm. For example, two electrocardiograms recently published by Richardson<sup>6</sup> (Figs 3 and 4 of his paper) present certain features which are not in agreement with pure *A-V* rhythm as it is commonly understood. Richardson's criteria for *A-V* rhythm include inversion of *P*, and to explain the upright *P* of his Figure 3, he suggests interference between the *S-A* and *A-V* nodes, both active. To carry this a step further, may not his Figure 3 represent partial intra-auricular block with continuous escape of the *A-V* node? One should note the striking resemblance of this record to Figure 9 of the present paper. Similarly, the arrhythmicity and protean contour of the *P* waves of his Figure 4 may well be due to intra-auricular block, accompanied, in this instance, by arrhythmic escape of the *A-V* node. Digitalis may have induced intra-auricular block in this patient. It is significant that the condition has been produced experimentally in dogs<sup>5</sup> by means of strophanthin.

Lewis has shown that in hearts driven at a constant rate the irregularity of the auricular waves from intra-auricular block is abolished by vagus excitation. In my experiments with the normally beating heart vagus stimulation promptly abolished intra-auricular block, for which sequential chamber contraction in response to one center, the *S-A* node, was substituted. The right vagus was employed exclusively in these experiments (Figs 18, 19, 20, 21, 22, 23).

Figures 1 to 11, inclusive, recorded from Dog 1, portray a remarkable series of events due to intra-auricular block. Figure 2 could not of itself be distinguished from *A-V* rhythm. It represents the stage when the auricular rate has slowed, but is still rhythmic. The *P* waves are buried in the *Q R S* group. Consideration of Figure 3, however, definitely sets aside the question of *A-V* rhythm. The auricle is now grossly arrhythmic, the interauricular intervals varying from 0.536 to 0.64 second. On the other hand, the interventricular intervals, exclusive of accidental beats, are equal. *R* bears no sequential relation to *P*. The latter is entirely independent of *R*, and whether it precedes, follows, or is submerged in *R* is purely a matter of accident. The only exception to this is seen when the impulse from the *S-A* node, by reason of its arrhythmicity, chances to arrive in the ventricle when the latter is not refractory. The ventricle then responds in the usual sequential fashion, disturbing temporarily the rhythmic *A-V* nodal control of the ventricle. Two examples of this appear in Figure 3. When *P* falls

6 Richardson Arch Int Med 29 253 (Feb) 1922

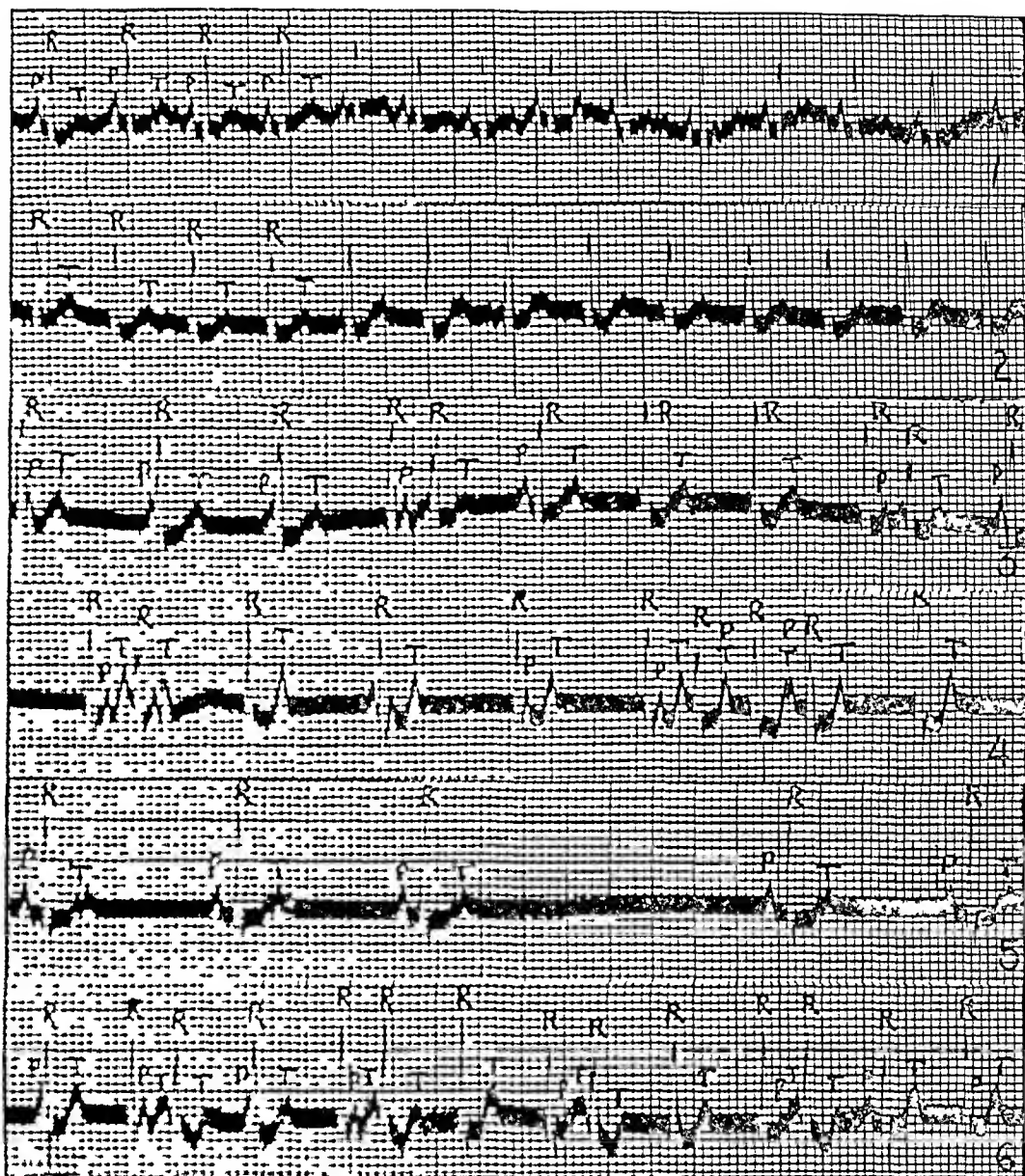


Fig 1 (D-I-02) —Rate, 160,  $P-R$ , 0.068,  $Q R S$ , 0.038 Unless otherwise stated, one scale division of abscissae equals 0.04 second, of ordinates,  $10^{-4}$  volt, in this and all succeeding figures Time measurements made with magnification of 18 diameters, accurate within a few thousandths of a second All experimental electrocardiograms from Lead II For full description see text

Fig 2 (D-I-10) —Rate, 160,  $Q R S$ , 0.056

Fig 3 (D-I-11) —Ventricular rate, exclusive of extra beats, 116, auricular rate circa 105,  $Q R S$ , 0.044,  $P-R$  of extra beats varies from 0.116 to 0.128

Fig 4 (D-I-12 B) —Ventricular rate, exclusive of extra beats, 97, auricular rate circa 89,  $Q R S$ , 0.054,  $P-R$  of extra beats varies from 0.104 to 0.168

Fig 5 (D-I-13) —Rate, 69,  $P-R$ , 0.096,  $Q R S$ , 0.048 Long pause exactly double the shorter diastole

Fig 6 (D-I-14 A) —Ventricular rate, exclusive of extra beats, 148, auricular rate circa 127,  $Q R S$ , 0.054,  $P-R$  of extra beats, 0.126





hythmic Figures 6, 7 and 8 show gradual recovery from intra-auricular block. In Figure 6 one sees a return of auricular arrhythmia, control of the ventricle by the *A-V* node at a rate of 148 per minute, and many extra beats of the ventricle as described in Figure 4. In Figure 7 the auricular arrhythmia has disappeared, but the auricle is slower than the ventricle, and the *S-A* node and *A-V* node still control auricle and ventricle, respectively. *P* is buried in *R*. Figure 8 shows the rates of auricle and ventricle nearly equal, *P* having emerged from *R*. The *P-R* interval is shorter than that of the control, however, and



FIG 12 (D-III-53-1) —*P-R*, 01, *QRS*, 0068

FIG 13 (D-III-54-1) —*P-R*, 0112, *QRS*, 0068

FIG 14 (D-III-55-1) —*P-R* of 006 does not represent transmission time

FIG 15 (D-III-61-5) —Rate, 83, *QRS*, 0112, usual *P-R* 0152, after long pause *P-R* 0128

the chambers still beat independently. Recovery from intra-auricular block is nearly complete in this record.

Figure 9 shows the auricle once more slowing from renewed intra-auricular block subsequent to a fresh injection of quinidin. Figure 10, recorded ninety seconds after Figure 9, shows complete intra-auricular block, auricular asystole, with ventricular autonomy at 45 per minute. Eventual termination of quinidin poisoning in ventricular fibrillation is revealed in Figure 11. Careful consideration of all the details dis-

played in this series of records emphasizes the point that, although as a rule all changes in function brought about in the various individual structures by quinidin poisoning proceed uniformly, at certain times single effects and different groups of effects predominate to the relative exclusion of others

A less striking occurrence of intra-auricular block, progressing only to the point of slight slowing of the auricular rate, was noted at one time in Dog 3. Figure 12 shows the character of the electrocardiogram at a rather late stage of poisoning. Five minutes later a considerable change in the character of *P* was seen, as shown in Figure 13. Figure

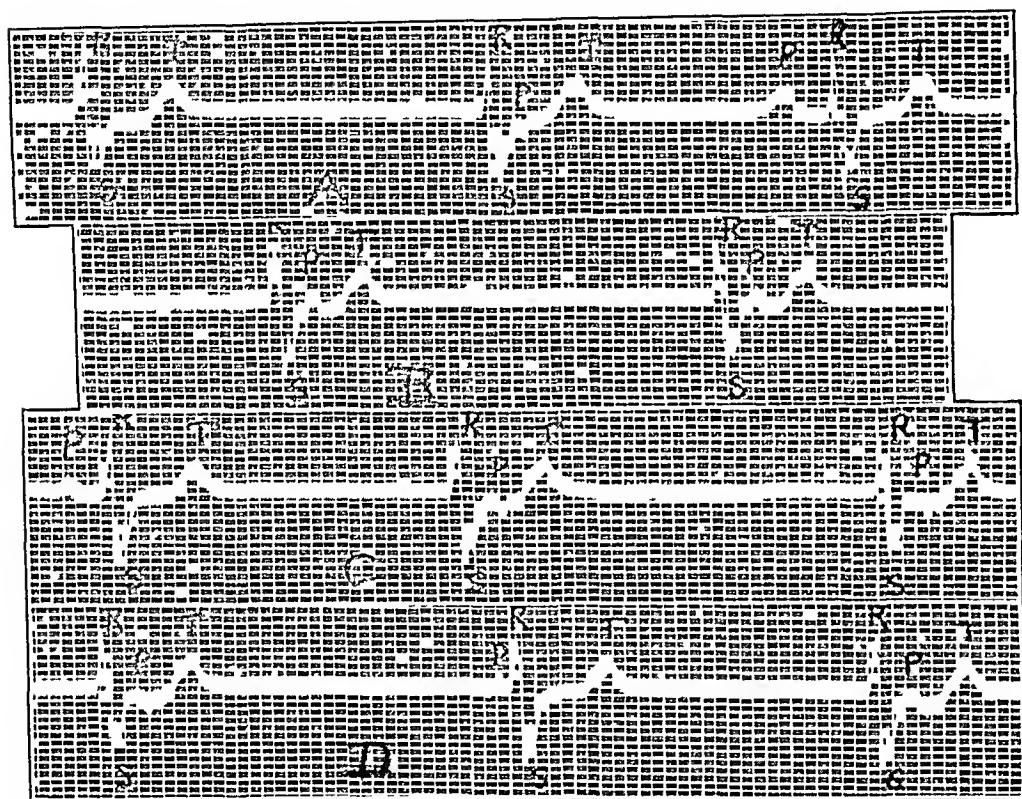


Fig 16 A (D-III-62) —Rate, 45, *Q R S*, 01

Fig 16 B

Fig 16 C

Fig 16 D

14 follows six minutes after Figure 13, and portrays slight slowing of the auricular rate. Figure 15 shows sino-auricular block at a still later stage of poisoning, and Figure 16 (A, B, C and D) depicts intra-auricular block in conjunction with a very slow *A-V* nodal rate of discharge. The last cycle in *A* and the first in *C* are examples of extra beats of the ventricle, comparable to those already described in connection with Dog 1.

Intra-auricular block appearing in a patient (Case 14) shortly after the resumption of normal mechanism is portrayed in Figure 17. The auricle is slowing, while the ventricle continues to respond at regular intervals to the *A-V* node.

The effect of vagus excitation on intra-auricular block is well shown in Figures 18 to 23, inclusive. In all instances the *A-V* nodal rate is inhibited to a greater or less degree with the beginning of stimulation. In all except Figure 19 the intra-auricular block is increased at the onset of stimulation, as shown by greater arrhythmia of the auricular beats. This is promptly succeeded, within a few cycles, by total abolition of the intra-auricular block and resumption of normal sequential chamber contraction by the whole heart. In Figure 19 the block is immediately decreased. Figure 21 is reproduced to show the rapid

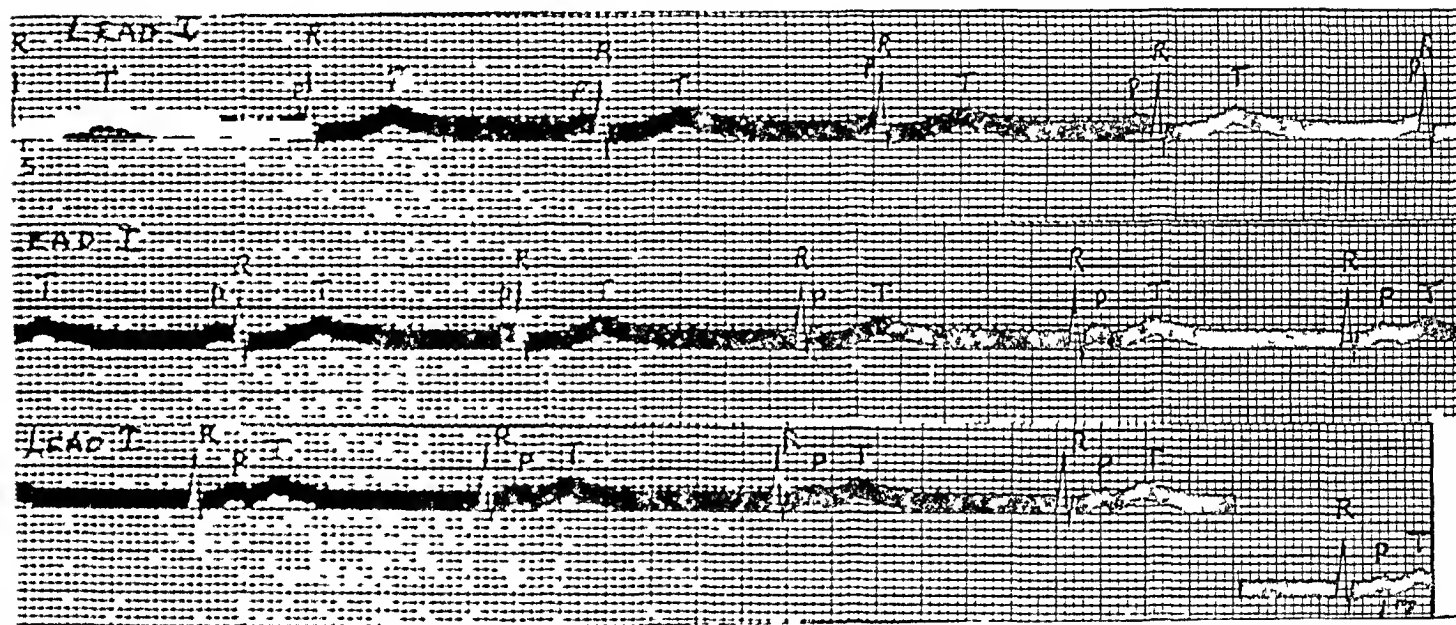


Fig. 17—Intra-auricular block in a patient (Case 14)

return of intra-auricular block five seconds after cessation of stimulation.

The fact that intra-auricular block could not be produced in guinea pigs is unexplained. *A-V* heart block and intraventricular block are the chief results of quinidin poisoning in these animals.

*Auriculo-Ventricular Conduction*—Most investigators have found that quinidin depresses *A-V* conduction in dogs, with which my results are in agreement. It is important to note that, in the naturally beating dog heart, this effect proceeds in direct proportion to the other changes simultaneously occurring in sino-auricular rate, intra-auricular conduction, and intraventricular conduction. It is never individually conspicuous, never advances farther than simple prolongation of the *P-R* interval. No dropped beat of the ventricle due to *A-V* block

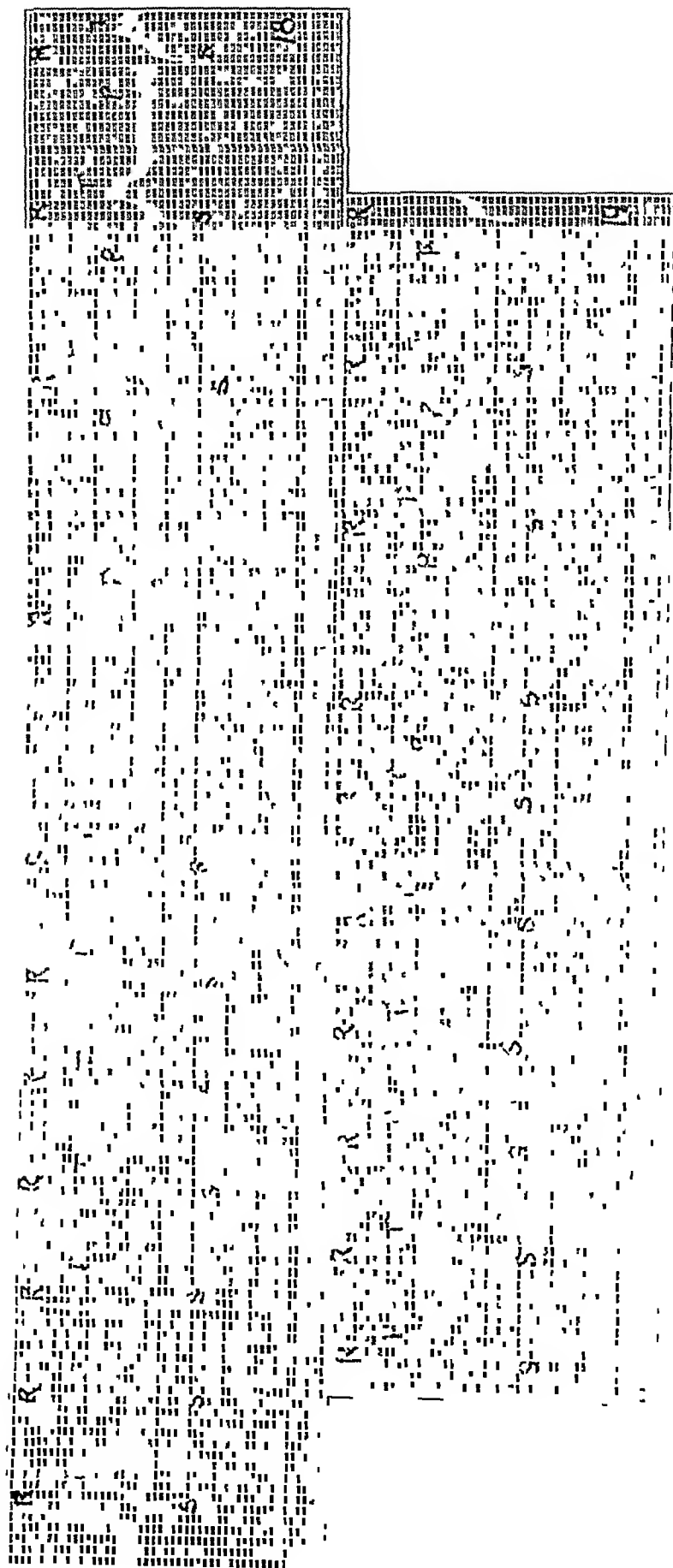


Fig 18 (D-V-12-1) — Intra-auricular block and vagus stimulation Signal marks beginning of stimulation Coil at 9 cm  
 Fig 19 (D-V-11) — As Figure 18 Coil at 9 cm

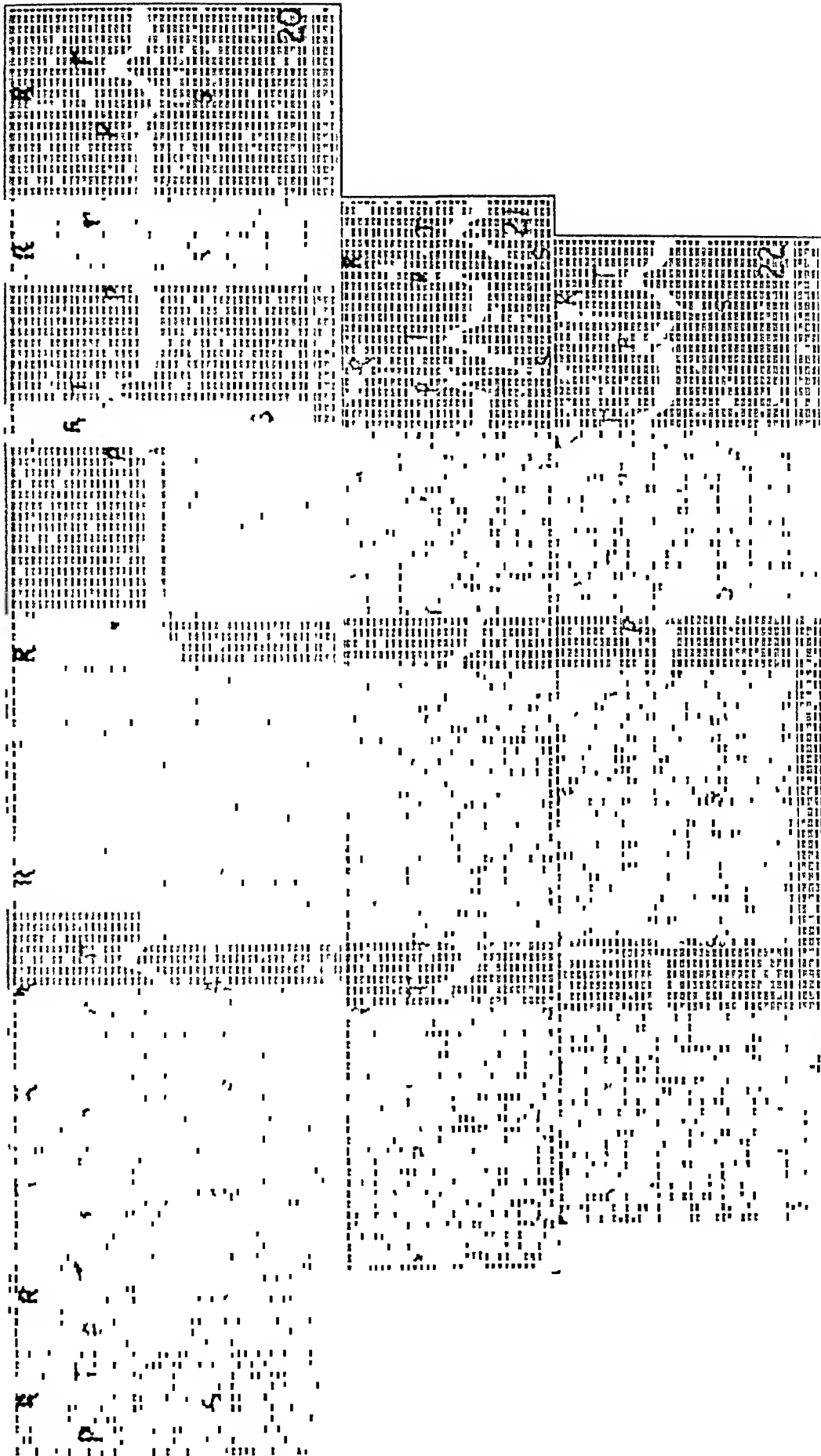


Fig 20 (D-V-11) —As Figure 18 Coil at 9 cm

Fig 21 (D-V-11) —Block returning, five seconds after cessation of stimulation

Fig 22 (D-V-14) —As Figure 18 Coil at 9 cm

occurred in my dogs, even in the very late stages of poisoning when complete branch block was well established

In the earlier stages of quinidin poisoning in guinea-pigs depression of *A-V* conduction progresses equally with other changes. As poisoning increases, however, a disproportionate effect on *A-V* conduction appears, which in my experiments reached, but never exceeded, the grade of 2:1 heart block. Schott<sup>2</sup> reports much higher grades of partial heart block in his pigs, a statement which has led many clinicians to avoid using quinidin and digitalis together. In only two cases, both reported by Hewlett and Sweeney,<sup>7</sup> has complete *A-V* heart block been regarded as the result of combined action of the two drugs, and in neither is it clear that digitalis alone might not have been responsible.

In my first few experiments with guinea-pigs, in which Schott's technic was closely followed, high grades of partial *A-V* heart block occurred rather early in the poisoning, progressing in one instance to complete *A-V* dissociation. It was immediately discovered, however, that the onset of block coincided closely with complete cessation of respiration, an event which always takes place very early in quinidin poisoning in the guinea-pig. In all subsequent experiments the factor of asphyxia was ruled out by supplying artificial respiration, with the result that *A-V* block completely disappeared from the early part of the experiment. Changes in *A-V* conduction were proportional to other changes throughout the experiment until a short time before death of the animal, when 2:1 response of the ventricle finally appeared in conjunction with bundle branch block. In each of these latter animals it was shown, prior to the administration of quinidin, that all grades of *A-V* heart block, including complete dissociation, could be produced by asphyxia alone. The precaution of ruling out asphyxia was not taken by Schott. From these results it is clear that the greater part of the *A-V* heart block reported by Schott was due to asphyxia, not to quinidin. It is true, however, that in the guinea-pig quinidin does produce an effect on *A-V* conduction out of proportion to changes in intra-auricular conduction in so far as the two are demonstrable when the heart is permitted to beat naturally, but the effect appears too late in the course of poisoning to be clinically applicable. So far as we have been able to determine by clinical and experimental means there is no direct contraindication to the use of quinidin and digitalis in combination. We have been in the habit of withholding quinidin until the full effect of digitalis has been secured simply because we believe digitalis to be the most essential weapon with which to combat cardiac decompensation, and because our best opportunity of studying the rôle

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7 Hewlett and Sweeney J A M A 77 1793 (Dec 3) 1921



of auricular fibrillation in cardiac failure is offered when all other factors contributing to that failure have been as far as possible removed

Figures 24 and 25 show the highest grade of *A-V* heart block obtained in guinea-pigs. The records are from different animals, registered 64 and 75 minutes, respectively, after the single dose of 0.67 gm quinidin. Artificial respiration was being maintained at the rate of 25 per minute. In addition to *A-V* block, both records show considerable delay in conduction through the right branch of the bundle.

*Intraventricular Conduction*—Disturbance of intraventricular conduction manifests itself initially in dogs and guinea-pigs by an increase in the *Q R S* interval which is generally comparable to changes in

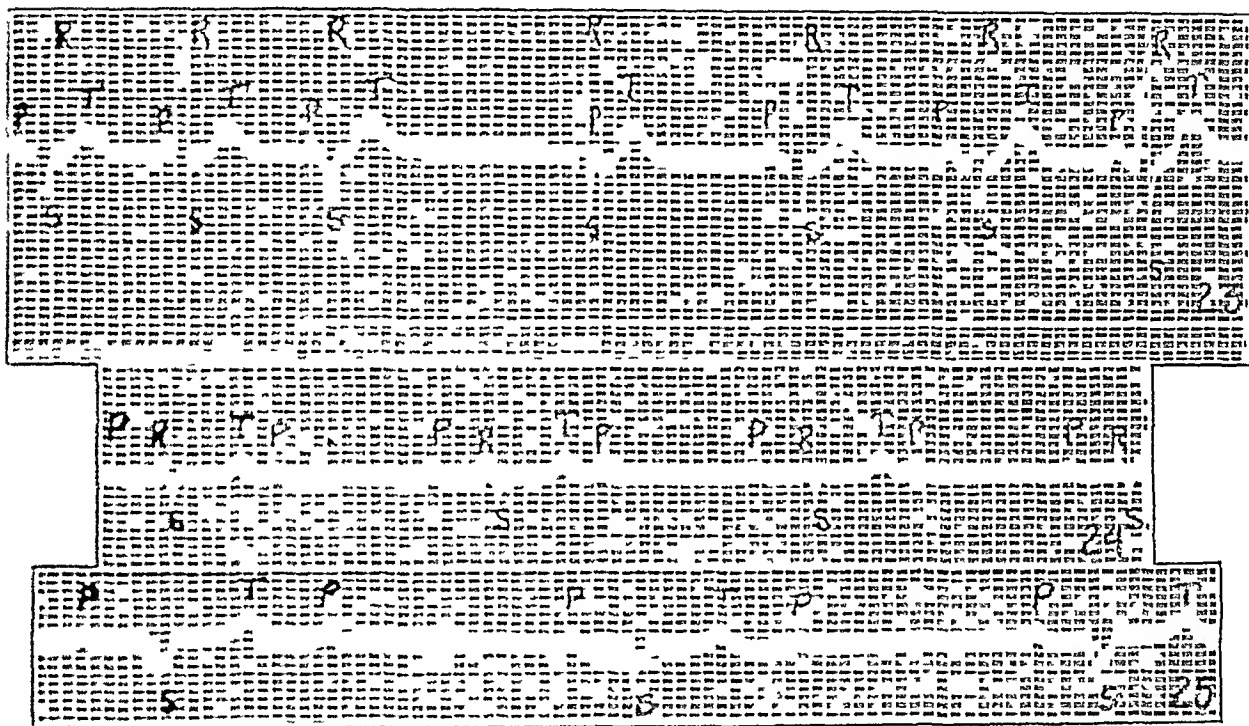


Fig 23 (D-V-15) — As Figure 18. Coil at 9 cm

Fig 24 (P-V-31-1) — 2. 1 response of the ventricle

Fig 25 (P-VII-20-2) — As Figure 24. (In this record ordinates do not exactly equal  $10^{-4}$  volt, resistance exceeds 2,000 ohms, and string overshoots slightly.)

intra-auricular and *A-V* conduction. With deeper poisoning, delay in conduction through one or both branches begins to appear. As I have stated in a previous paper,<sup>8</sup> this delay in branch conduction is to be explained on the basis of differential widening of the refractory periods of the two main divisions of the bundle. Rapid development of the dextrocardiogram or levocardigram, or alteration of the dextrocardio-



gram and levocardiogram, follows single and repeated injections of quimdin, with eventuation in complete bundle branch block

Figures 26 to 30, inclusive, portray the development of right bundle branch block in Dog 5. The control (Fig 26) shows that the dextro-

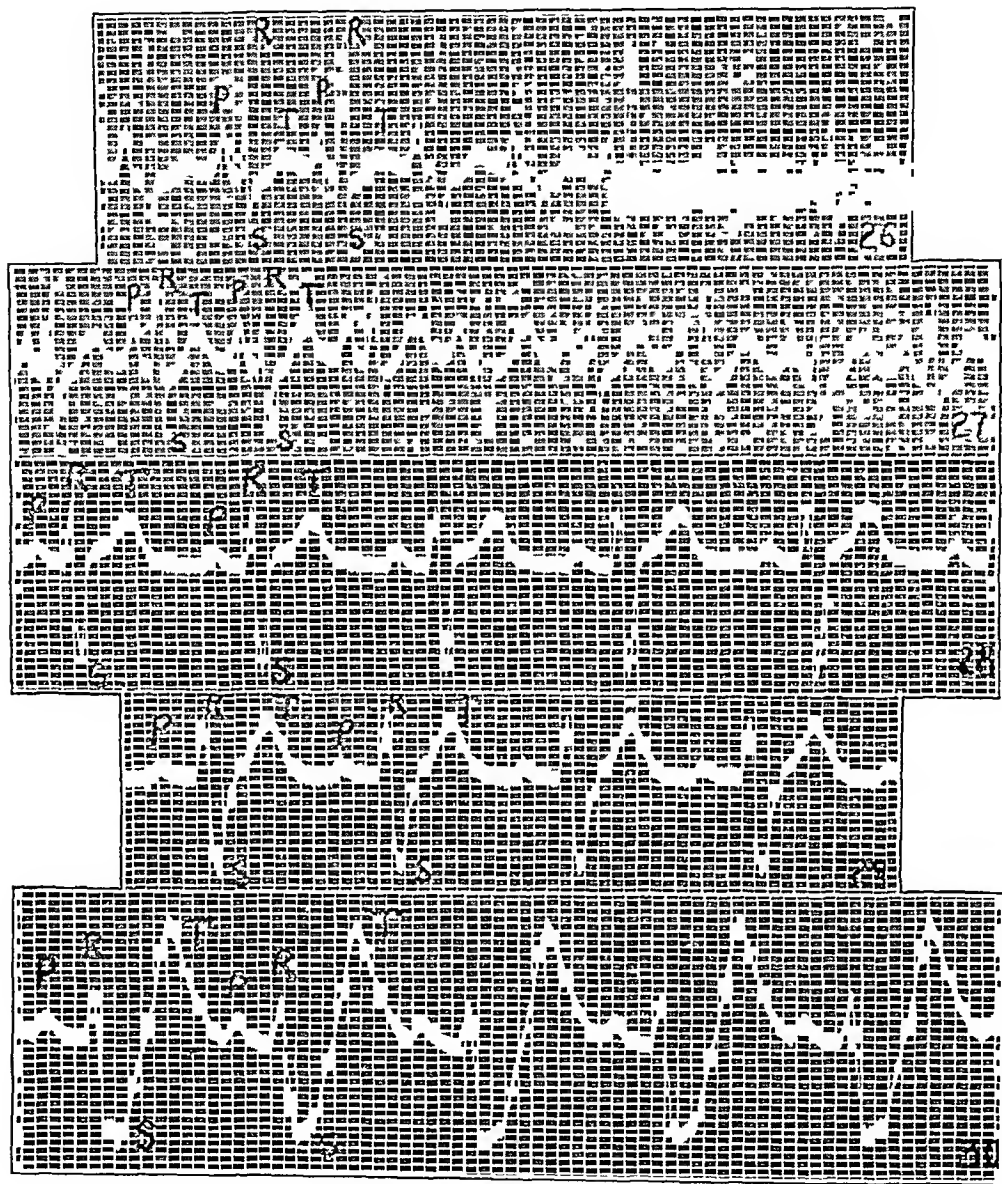


Fig 26 (D-V-02) —Rate, 192, *P-R*, 0.072, *Q R S*, 0.042

Fig 27 (D-V-10) —Rate, 172, *P-R*, 0.08, *Q R S*, 0.042

Fig 28 (D-V-21-1) —Rate, 107, *P-R*, 0.112, *Q R S*, 0.08

Fig 29 (D-V-22-4) —Rate, 107, *P-R*, 0.15, *Q R S*, 0.12

Fig 30 (D-V-22-5) —Complete right bundle branch block

cardiogram is normally predominant. Figure 27 shows the rapid advancement of the levocardiogram (lengthened refractory period of the right branch) immediately following the initial injection of 0.1 gm quimdin. Figures 28, 29 and 30 display further gradations in the

process with increasing dosage. A similar series of steps in the development of left bundle branch block (Dog 2) are presented in Figures 31 to 35, inclusive.

Differential widening of the refractory periods of both the right and left branches of the bundle is depicted in a series of records from Fig 5 (Figs 36 to 44, inclusive). The disturbance of conduction develops first, and remains of higher grade throughout, in the left

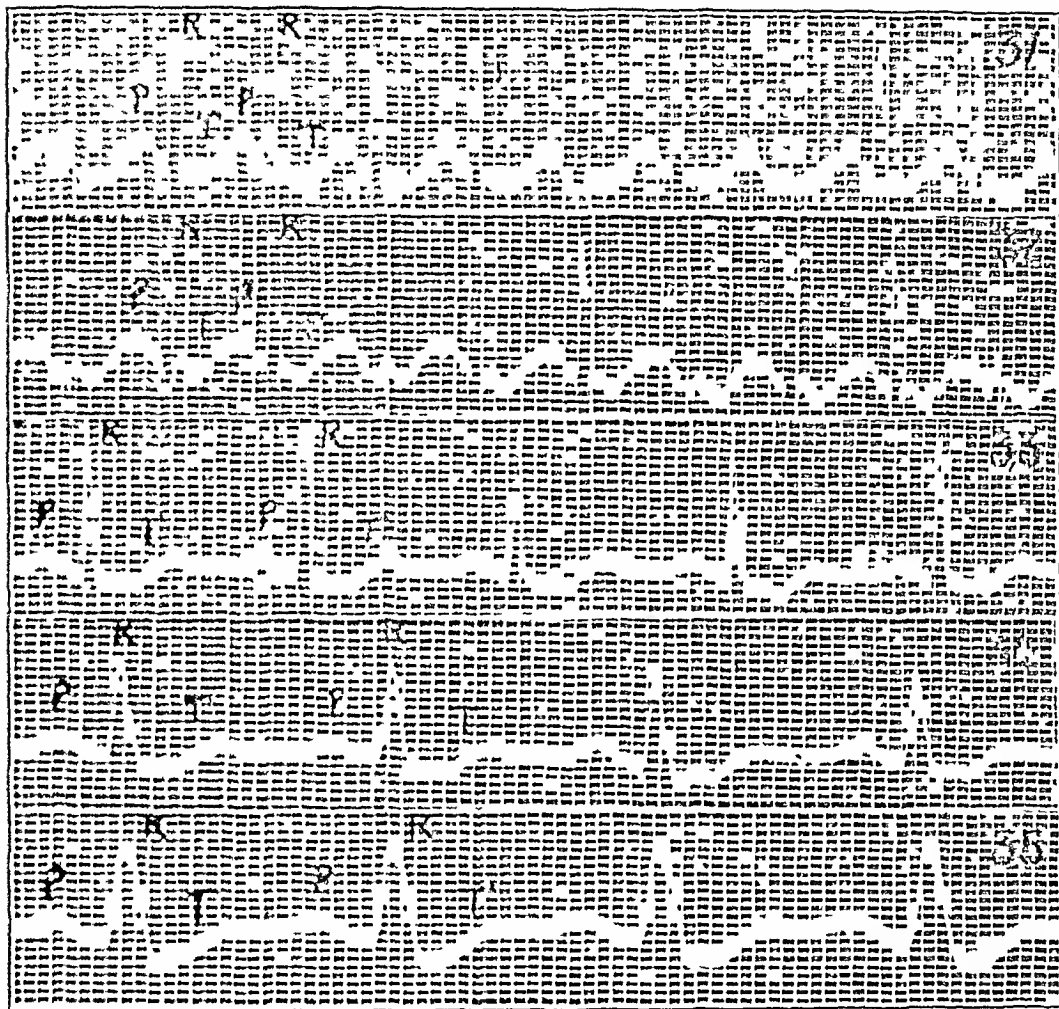


Fig 31 (D-II-02) —Rate, 202, *P-R*, 0.084, *QRS*, 0.04

Fig 32 (D-II-12-2) —Rate, 194, *P-R*, 0.084, *QRS*, 0.04

Fig 33 (D-II-41-1) —Rate 97, *P-R*, 0.12, *QRS*, 0.048

Fig 34 (D-II-51-3) —Rate, 81, *P-R*, 0.16, *QRS*, 0.084

Fig 35 (D-II-54-5) —Complete left bundle branch block

branch. It is of interest to note, in Figure 40, that the long refractory period of the left branch is compensated when a ventricular beat is dropped, for the ensuing complex shows nearly synchronous fusing of the dextrocardiogram and levocardiogram. Deficient branch conduction appears because the refractory period of the branch is longer than that of the *A-V* node. In Figure 41 the refractory period of the branch

has become too long to be compensated for by one dropped beat of the ventricle

Left bundle branch block appearing in a patient (Case 27) after a total of 6 gm quinidin is displayed in Figure 45. It disappeared shortly after withdrawal of the drug (Fig 46). One similar case has been recorded in the literature, that of White, Marvin and Burwell.<sup>9</sup>

*Changes in the T Wave*—Many variations of the end deflection *T* have been ascribed to quinidin. In analyzing my experimental curves

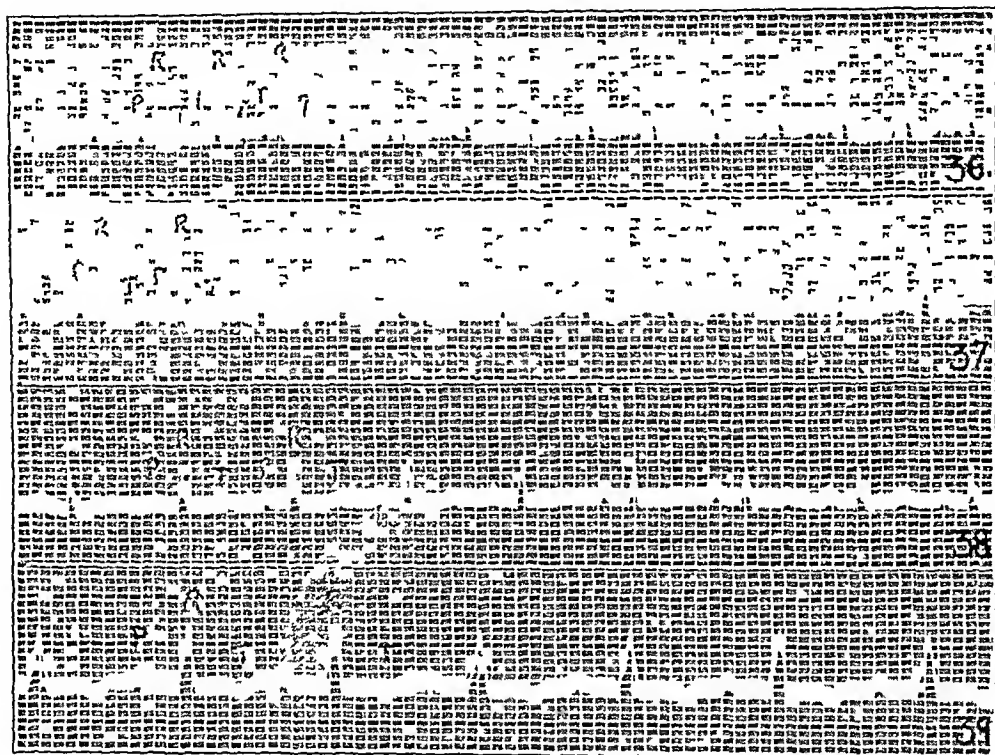


Fig 36 (P-V-02)—Rate, 272, *P-R*, 0.052 *QRS*, 0.016

Fig 37 (P-V-16-1)—Rate, 220, *P-R*, 0.076, *QRS*, 0.028

Fig 38 (P-V-19-3)—Rate, 164, *P-R*, 0.088, *QRS*, 0.036

Fig 39 (P-V-24-1)—Rate, 127, *P-R*, 0.156, *QRS*, 0.072

I have been struck by the fact that in every case the voltage of *T* has altered early in the experiment, and furthermore, its voltage has always initially increased in the direction which will conform with the branch lesion to be found in the late stages of poisoning. Comparing Figure 27, from a dog which eventually developed right bundle branch block, with Figure 32, from a dog which developed left bundle branch block, it is found that, whereas in the former the effect of the first injection of quinidin was to increase the voltage of *T* by 300 microvolts

<sup>9</sup> White, Marvin, and Burwell. Boston M & S J 185:647 (Dec 1) 1921

( $3 \times 10^{-4}$ ), in the latter the first effect was a deepening at *T*. A similar effect was observed in Fig 5. It will be recalled that this animal showed greater prolongation of the refractory period of the left than of the right branch, although that of both branches was widened. Reference to Figure 37 shows that an originally upright *T* was inverted by the first quinidin injection. It later became isoelectric, then upright,

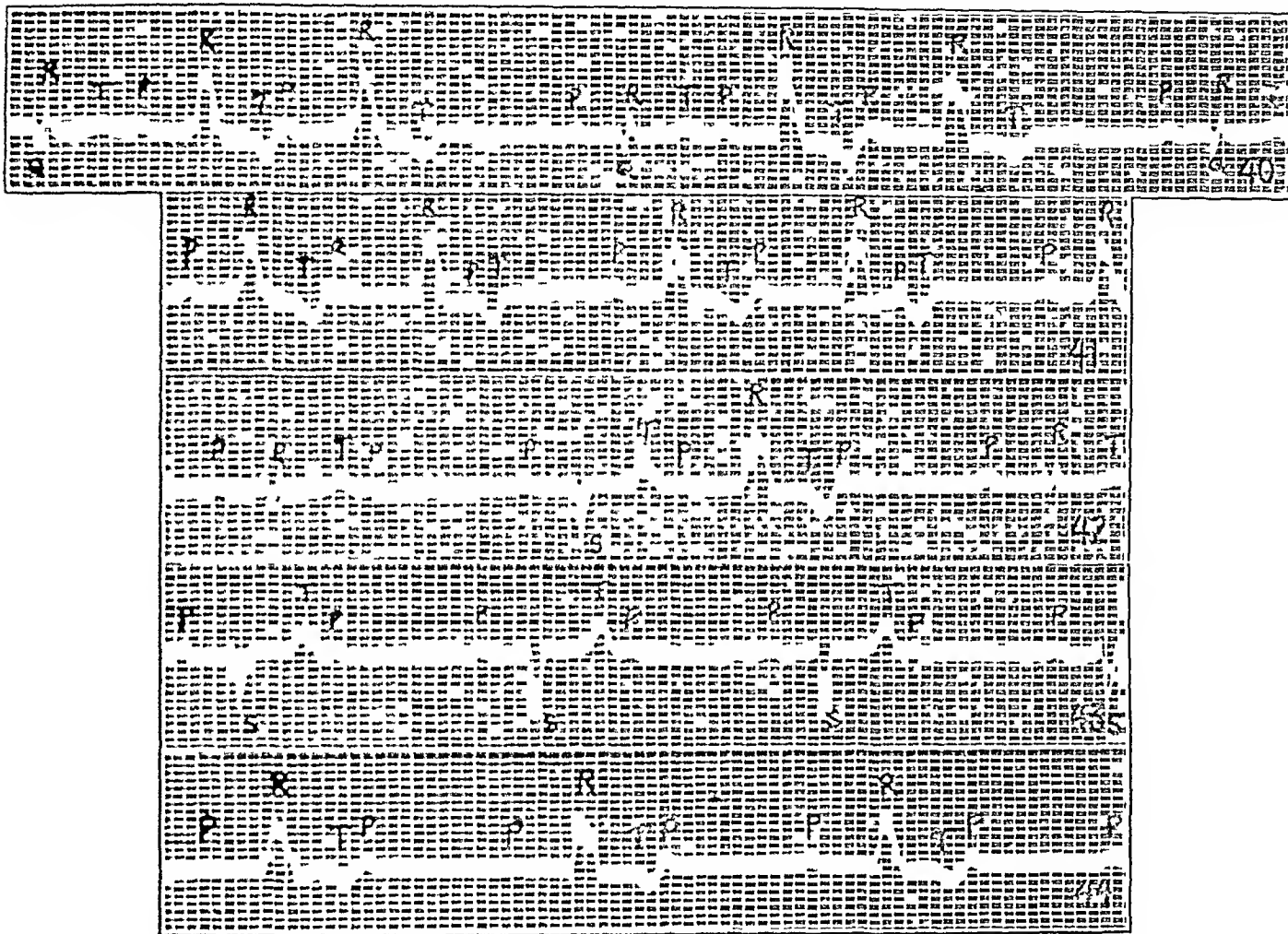


Fig 40 (P-V-27-1) —Long refractory period of the left branch is compensated when ventricular beat is dropped

Fig 41 (P-V-28-1) —Complete left bundle branch block, partial *A-V* block

Fig 42 (P-V-30-2) —Differential widening of refractory periods of right and left branches

Fig 43 (P-V-32-2) —Recovery of left branch, involvement of right branch

Fig 44 (P-V-33-2) —Eventuation in 2:1 *A-V* block and complete left bundle branch block

and again inverted, apparently fluctuating with the refractory period differences of the branches

The exact nature of the *T* wave has never been fully elucidated. Wilson and Herrmann<sup>10</sup> believe that the exaggerated *T* wave which

<sup>10</sup> Wilson and Herrmann Arch Int Med 26 153 (Aug) 1920

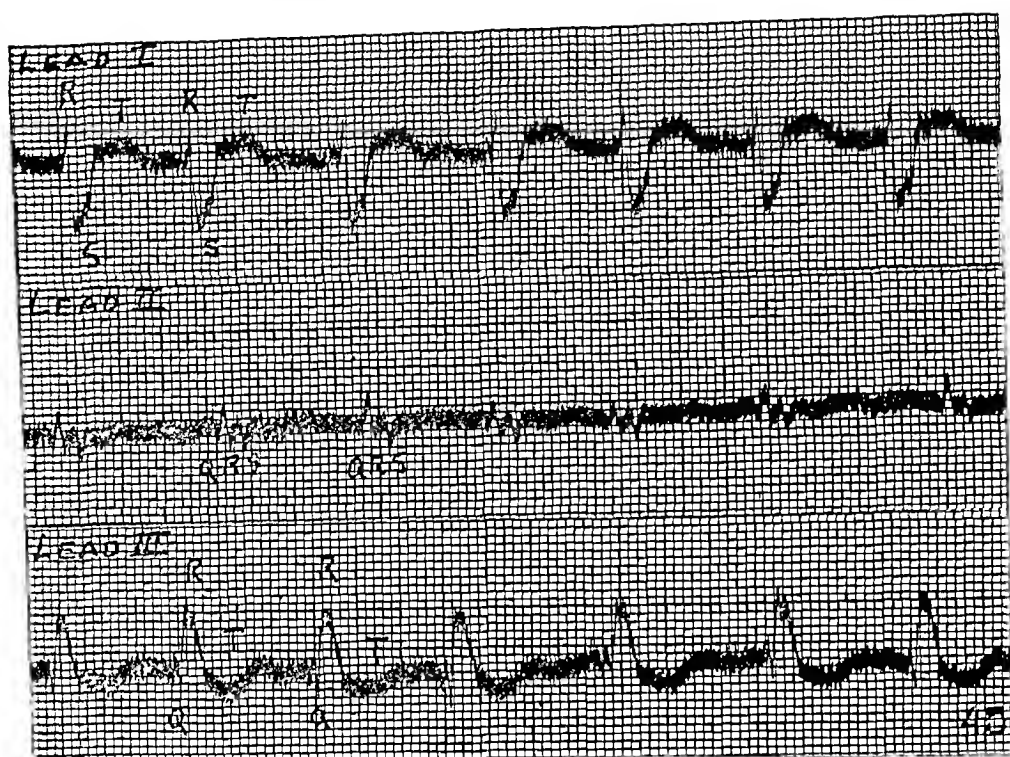


Fig 45—Left bundle branch block in a patient (Case 27)

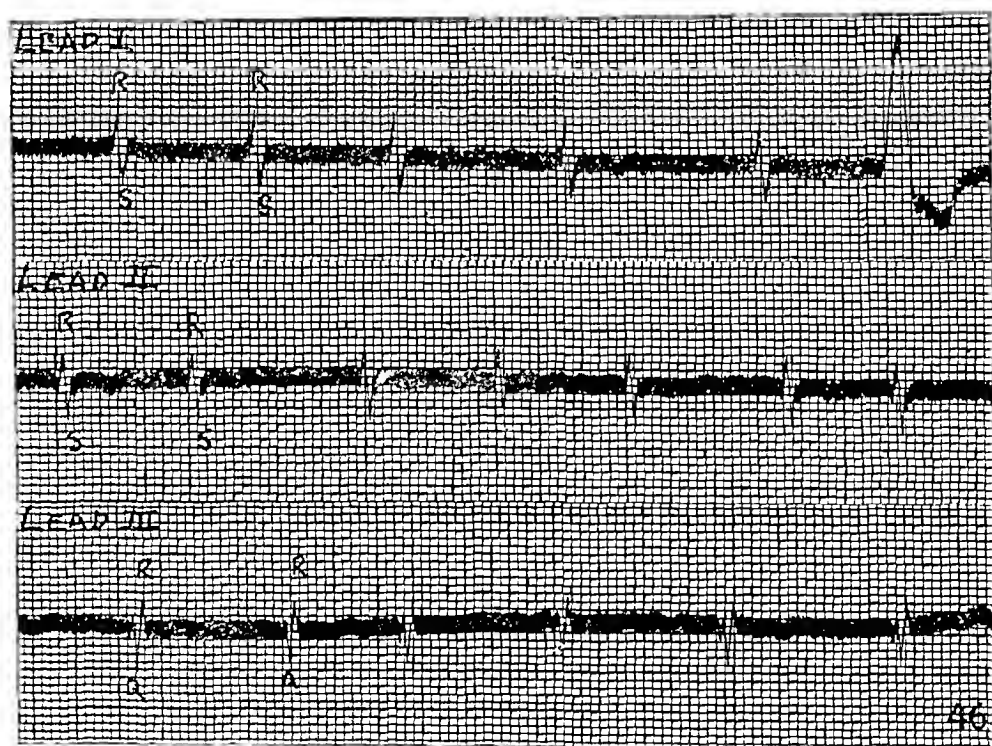


Fig 46—Recovery of conduction in left branch in Case 27 after withdrawal of quinidin



appears in Lead II of the dog's electrocardiogram after division of the right branch of the *A-V* bundle is due to early deactivation of the left ventricle in comparison with the right ventricle, and vice versa. The observations above described suggest that changes in the character of *T* under quinidin are the first delicate indications of earlier deactivation of one or the other ventricle, hence the initial indications of lengthening of the refractory period of the right or left branch of the *A-V* bundle.

*Action on the Vagi*.—The careful observations of Lewis and his co-workers<sup>1</sup> demonstrate conclusively that quinidin, in doses comparable to those used clinically, exerts a striking parietic effect (peripheral) on the vagi. My own observations were incidental to the examination of other effects. They were made on hearts controlling their own rate of beating, and the results are therefore complicated by slowing due directly to quinidin, and by other factors. Nevertheless, a definite qualitative parietic effect was demonstrable. In one animal the minimal effective stimulus was noted with the secondary coil at a distance of 8 cm. from the primary. Twenty minutes after the first injection of 0.1 gm. the coil was moved to 4 cm. for the minimal effective stimulus. Three minutes after the second injection of 0.1 gm., before time for recovery had been allowed, 0.5 cm. was the coil distance for minimal vagus effect. No response whatever could be obtained after the third injection of 0.1 gm. A result similar to this was noted in one other animal. The so-called "paradoxical action" described by Lewis was not encountered.

*Cause of Death from Quinidin*.—All my dogs died of ventricular fibrillation, respiration stopping only a few minutes before death. As other workers have observed, the greater the fractionation of dosage, the further is fatal poisoning postponed. Guinea-pigs, if let alone, die an early death from apnoea due to rapid failure of automatic breathing. If artificial respiration be supplied, however, these animals resist the poison vigorously. In order to observe the late effects of poisoning in one of the pigs it was necessary to administer a second dose of 0.67 gm. Death occurs in these animals, never by ventricular fibrillation, but through gradual slowing and final inhibition of the whole heart.

Aside from fatal terminations due to emboli, which will be discussed in a subsequent paper, it is probably too early to make the statement that quinidin has been directly responsible for the death of any patient. There are many factors to be accounted for in sudden cardiac death. If the drug shall be held solely responsible for sudden fatality, the event must be occasioned by some disastrous effect on the cardiac mechanism. Two suggestions appear in Lewis' paper: (1) the possibility, under quinidin, of long standstill of the ventricle consequent upon a slight rise in auricular rate, and (2) slowing, or actual standstill, of

the ventricle at the moment of resumption of normal sino-auricular rhythm. The question may not find an answer until continuous electrocardiograms are recorded just before and during death supposedly due to quinidin.

Brief reference may be made to the recent paper of Jackson, Friedlander and Lawrence,<sup>11</sup> concerning the pharmacology of quinidin. For some reason, these authors have disregarded the experimental work of Lewis and his associates, with which a great many of their results are not in agreement. After careful comparison of the methods adopted by the two groups of investigators in reaching their conclusions, one is strongly inclined to believe that none of the positions taken by Lewis has been essentially modified.

#### SUMMARY AND CONCLUSIONS

Quinidin sulphate exerts the following actions on the normally beating heart of the dog and guinea-pig.

- 1 It may temporarily accelerate, but ultimately retards, the rate of impulse discharge from the pacemaker, regardless of whether the latter be situated in the *S-A* node or the *A-V* node. This is probably a direct effect on the Purkinje structures.

- 2 It produces, in the dog, depression of intra-auricular conduction leading to partial or complete intra-auricular block. This is described for the first time in the heart beating spontaneously. A relationship between intra-auricular block and so-called "sino-auricular block" is suggested. Criteria are presented which serve to distinguish intra-auricular block from *A-V* rhythm. It is demonstrated that vagus stimulation abolishes intra-auricular block.

It produces, in the guinea-pig, no demonstrable evidence of interference with intra-auricular conduction.

- 3 It depresses *A-V* conduction, which, in the dog, proceeds strictly in accordance with other functional changes.

In the late stages of poisoning in the guinea-pig it produces a disproportionately great effect on *A-V* conduction, leading to 2:1 response of the ventricle, never higher.

- 4 It produces delay of intraventricular conduction. This is evidenced at first solely by lengthening of the *Q R S* interval, later, by differential widening of the refractory periods of the right and left branches of the *A-V* bundle.

- 5 It produces remarkable changes in the voltage and sign of the *T* wave. Evidence is found which suggests that these changes are directly related to alterations in intraventricular conduction.

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<sup>11</sup> Jackson, Friedlander and Lawrence. *J. Lab. & Clin. Med.* 7: 311 (March) 1922.

- 6 It produces, in the dog, a high degree of vagal paresis
- 7 It induces death, in dogs, by ventricular fibrillation, in guinea-pigs, by gradual inhibition of the whole heart
- 8 Intra-auricular block from quinidin is described in a patient
- 9 The clinical use of quinidin in conjunction with digitalis is discussed
- 10 Left bundle branch block from quinidin is described in a patient
- 11 Some possible relationships of quinidin to sudden cardiac death are pointed out



# AN EXPERIMENTAL AND CLINICAL STUDY OF QUINIDIN SULPHATE II CLINICAL<sup>1</sup>

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CLEVELAND

In the short time that quinidin has been under intensive investigation, a considerable number of facts regarding its action and uses have become generally apparent. It is well recognized that quinidin therapy is not applicable outside the field of disordered cardiac mechanism, and is furthermore limited to two general classes of disorder within that field: (1) The paroxysmal tachycardias, including premature contractions occurring singly or in groups, (2) disorders due to circus movement within the auricle, comprising, (a) auricular flutter, (b) auricular fibrillation.

Clinical experience with arrhythmias of the first class is still extremely meager. Hamburger<sup>1</sup> mentions a case of auricular paroxysmal tachycardia, but reserves discussion until more extended observations shall have been made. Boden<sup>2</sup> states that quinidin was tried with favorable results in twenty-two cases showing premature beats, mostly ventricular in origin, and that in six cases of atrioventricular or ventricular paroxysmal tachycardia cessation of paroxysms was secured four times, and great diminution of rate twice. White, Marvin and Burwell<sup>3</sup> noted abolition of ventricular premature beats, in one case, during continued medication with small doses of quinidin. Smith<sup>3</sup> reports excellent results in seventeen cases of premature beats and one case of paroxysmal tachycardia. At this point I wish to report a single case.

## REPORT OF CASE

*History*—(Case 20 [87796]) I W, a girl, aged 16, had suffered from air hunger on exertion ever since she could remember. After climbing stairs, for example, she felt very dizzy, faint, short of breath and was conscious of unwonted fluttering of her heart. She had never noticed edema. She gave an ample history of previous infections, numbering among them diphtheria, typhoid fever, scarlet fever, measles, pertussis, chronic otitis media, numberless attacks of sore throat, and a questionable story of variola. Clinically, she presented the picture of chronic myocarditis and mitral stenosis, with clearly demonstrable enlargement of both the right and left ventricles and right auricle. The rhythm seemed to be fundamentally under sino-auricular control, but was being con-

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<sup>1</sup> A detailed list of references will not be attempted. For comprehensive bibliographies see Hamburger J A M A 77 1797 (Dec 3) 1921 Oppenheimer and Mann J A M A 77 1800 (Dec 3) 1921 Wolferth M Clinics N America 5 783 (Nov) 1921 White, Marvin and Burwell Boston M & S J 185 647 (Dec 1) 1921.

<sup>2</sup> Boden and Neukirch Deutsch Arch f klin Med 136 181, 1921.

<sup>3</sup> Smith J A M A 78 877 (March 25) 1922.

tinually interrupted by premature contractions which occurred sometimes singly, often in small groups, and frequently constituted long paroxysms of tachycardia. The electrocardiogram (Fig 1) proved the origin of the premature beats and paroxysms to be at the same point in the wall of the right ventricle, and showed that the ectopic impulses were occasionally retrograde to the auricle. The patient was put to bed and quinidin therapy carried out, as follows: December 3, 0.33 gm (5 grains), December 4, 1 gm (15 grains), December 5, 1 gm

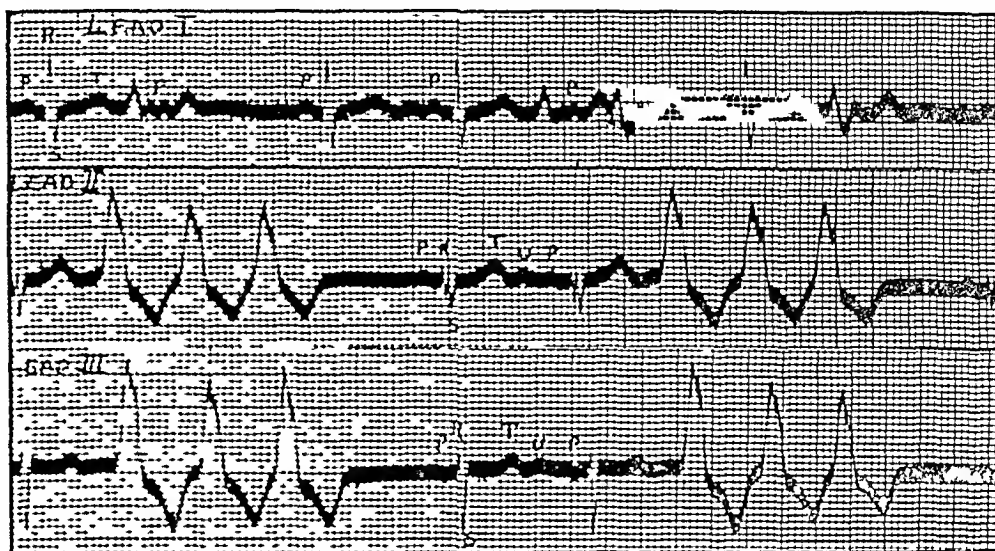


Fig 1—Electrocardiogram of I W (Case 20, 87796) showing origin of premature beats and paroxysms. In this and all succeeding figures one scale division of abscissae equals 0.04 second, of ordinates,  $10^{-4}$  volt.

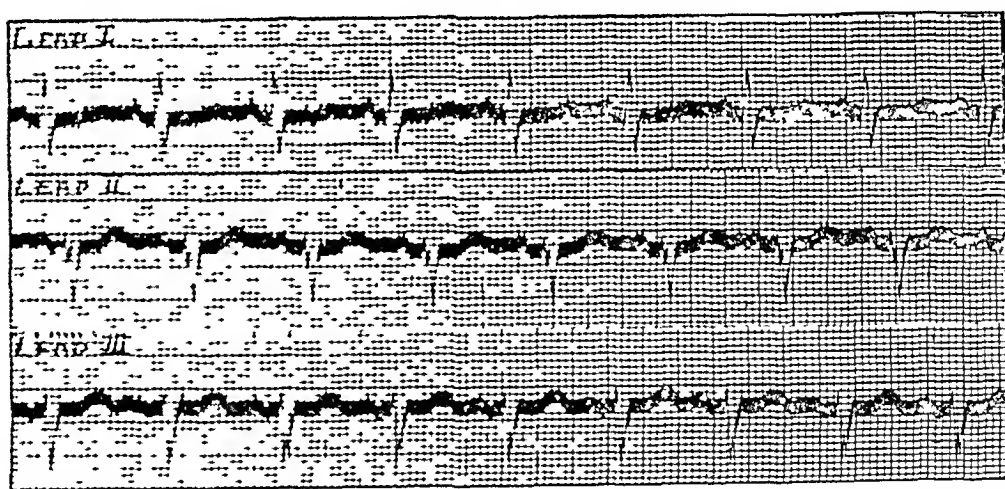


Fig 2—Electrocardiogram of I W showing absence of premature beats.

(15 grains), December 6, 1.67 gm (25 grains), December 7, 1 gm (15 grains), December 8, 1 gm (15 grains), December 9, 1 gm (15 grains).

December 7, after 5 gm of the drug had been taken, the arrhythmia was observed to be absent. Whereas before it had been impossible to secure an electrocardiogram without the appearance of great numbers of the premature beats, it was now easy to do so (Fig 2). December 9, the efficacy of the treatment was tested by having the patient climb several flights of stairs, immediately after which an electrocardiogram was made (Fig 3). It will be seen that the paroxysms are prominent. The conclusion was that, although

the paroxysms could be abolished so long as the patient remained at rest, the dosage required to control them during exercise was too high to be practicable in continued use, and the attempt was, therefore, abandoned

It is probable that disordered mechanism was in this case one of the factors contributing to the patient's disability, but inasmuch as the disability appeared only during exercise, when the tachycardia could not be controlled adequately, the relative contribution could not be gaged accurately. Quinidin directly depresses the excitability of heart

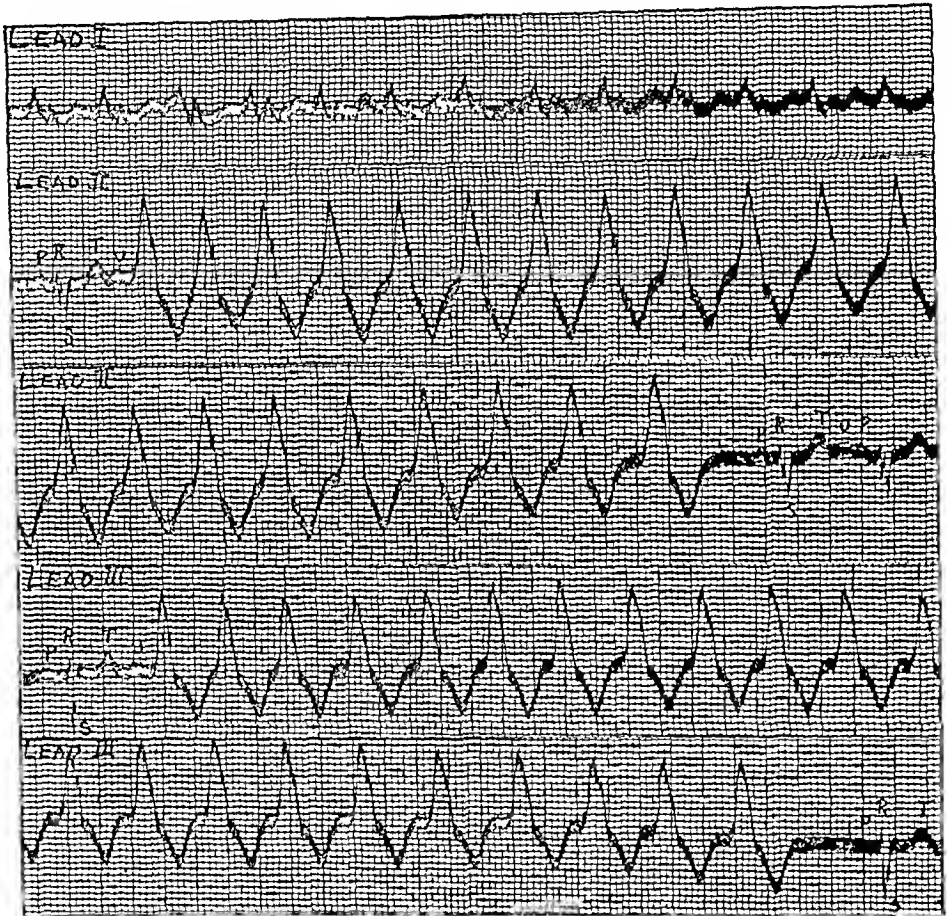


Fig 3—Electrocardiogram of J W. Lead I shows a continuous paroxysm of ventricular tachycardia. Leads II and III show the beginning and end of paroxysms. Rate of tachycardia, 136 per minute.

muscle, and therefore may inhibit any ectopic focus of origin of impulses to a degree sufficient to prevent paroxysms of tachycardia. The action is clearly analogous to the experimental observation, concurred in by most investigators, that the threshold for the production of premature beats or auricular fibrillation is tremendously exalted by quinidin. Failure was encountered in the case described because the heart muscle was not susceptible, within safe limits of dosage, to this action of quinidin. In other cases of similar character the paroxysms

may not only be terminated immediately, but permanently prevented by giving small doses of quinidin. It is obvious that the result can never be predicted in any case.

Certain observations made by Levy<sup>4</sup> are pertinent to this discussion. In one patient he found ectopic ventricular tachycardia occurring among the mechanisms transitional between auricular fibrillation and normal rhythm, and later in the same patient, paroxysms of auricular tachycardia interrupting the established normal mechanism. In other patients ectopic ventricular tachycardia was observed three times. No explanation of this contradictory occurrence suggests itself, unless it be that small doses of the drug may, in certain instances, produce a preliminary lowering of the threshold of excitability, to be succeeded by later exaltation of the threshold under the influence of larger doses.

It is in arrhythmias of the second class, auricular flutter and auricular fibrillation, that quinidin therapy has its widest application. At this point it is necessary to refer briefly to the new theory of circus movement, so ably supported by Lewis and his co-workers<sup>5</sup>. This theory has already been accepted widely, that it will require material revision seems unlikely. By means of it we are made to appreciate the fact that flutter and fibrillation are essentially of the same character, differing only in that in the former the circulating wave of excitation travels always in a constant anatomic path, whereas in the latter it travels on a path which varies in greater or less degree from cycle to cycle. It is to be expected, therefore, that if quinidin modifies the underlying circus movement it will affect flutter and fibrillation in identical ways. This expectation cannot be tested fully until our present acquaintance with the action of quinidin in chronic auricular flutter has been extended considerably. The theory of circus movement is thoroughly competent to explain the mechanism of action of quinidin in abolishing auricular fibrillation<sup>6</sup>—a phenomenon which would otherwise be most obscure. It is remarkable that restoration of a normal cardiac mechanism is secured in almost exactly 50 per cent of all cases, a fact which of itself strongly suggests that restoration depends solely on some fundamental relation between the action of the drug and the pathologic physiology of the auricular muscle. Conversely, the action of the drug seems to offer additional proof of the theory, for the gradual transition, seen in clinical electrocardiograms, from fine waved fibrillation through coarse waved fibrillation, impure flutter and pure flutter, to normal rhythm, strongly suggests that fibrillation and flutter are due

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<sup>4</sup> Levy, *Proc Soc Exper Biol & Med* **19** 88, 1921

<sup>5</sup> Lewis, *Heart* **7** 127, 131, 191, 247, 293, 1920, **8** 193, 1921

<sup>6</sup> Lewis, Drury, Ilescu and Wedd, *Brit M J* **2** 514 (Oct 1) 1921, *Heart* **9** 55, 1921

to the same fundamental cause, and that fibrillation is simply an advanced degree of impure flutter

A review of the literature establishes the fact that in any given case of auricular fibrillation one can never predict whether or not quinidin will be able to restore a normal mechanism, or, once restored, to maintain it. With this fact my own clinical experience with quinidin is in complete agreement. Incidental circumstances, such as the character of the cardiac lesion, the degree of decompensation, the duration of the disordered mechanism, the age of the patient, etc., are not essentially related to failure or success with quinidin. Many examples of this appear among the cases selected for report. If Case 2 be compared with Case 17, one finds that in both patients high arterial pressure was a prominent feature, associated with chronic myocardial disease and chronic nephritis. Case 2 retained auricular fibrillation after 11 gm of the drug had been given, whereas Case 17 responded with a normal rhythm after 13 gm. The outstanding lesions in Cases 22 and 24 was primary myocardial disease, the former was not affected by 17 gm of quinidin, but sequential rhythm was easily secured in the latter by 2 gm. Comparison of Case 19 with Case 25 shows that in both cases chronic endocarditis of the mitral valve was present, Case 19 underwent no change in mechanism after 16 gm of the drug had been given, whereas Case 25 responded with a normal rhythm after the last course of 13.33 gm. In Case 17 auricular fibrillation soon recurred, and normal mechanism was not again restored by 8.33 gm. Case 27, of similar type, responded to the drug with disturbance in intraventricular conduction<sup>7</sup> before any effect on the circus movement was manifest. That fibrillation of very long duration may often be abolished with the greatest ease was well exemplified by Case 24. The disordered mechanism was known to have persisted in this patient for five years, yet a total of 2 gm of quinidin was sufficient to restore a sequential mechanism. One of the best therapeutic results was secured in Case 14, although the patient declared that he had had an "uneven pulse" for at least ten years. In this patient 5 grains of quinidin every forty-eight hours are sufficient to maintain the normal rhythm, whereas in Case 24 from 15 to 20 grains are required in twenty-four hours. Several of our patients over 70 years of age were among those most susceptible to quinidin therapy. The conclusion of Drury and Ilescu<sup>8</sup> that both successful and unsuccessful cases form heterogeneous groups has become universal.

The outstanding contribution made to clinical cardiology by the introduction of quinidin is the opportunity which it affords of studying

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<sup>7</sup> This issue, page 32, Figure 45

<sup>8</sup> Drury and Ilescu. *Brit M J* 2 511 (Oct 1) 1921.

quantitatively the rôle of auricular fibrillation in myocardial failure. As clinicians, we have often been at a loss in attempting to evaluate the disordered mechanism. In most instances it has been impossible to determine whether auricular fibrillation was merely one of a number of relatively insignificant details in the clinical picture of cardiac decompensation, or whether it contributed directly to the altered dynamics of the circulation. By means of quinidin we can reach a solution of this problem, for in every case in which auricular fibrillation can be split off by selective drug action from other possible factors in heart failure we are able to gain an unobstructed view of its participation in the production and maintenance of decompensation. We have been provided with a therapeutic test comparable to that which we apply to the problem presented by the patient whose an hunger may be due to pulmonary emphysema, to bronchiolar hypertonus, or to both. If the question cannot be answered by physical signs alone, we may readily solve it by observing the effect of epinephrin on the physical signs, vital capacity, and subjective symptoms. Similarly, if a patient's heart failure be due to high arterial pressure, to auricular fibrillation, or to both we may evaluate the contribution of the disordered beat by substituting for it a normal cardiac mechanism.

In order to gain a comprehensive conception of the contribution of auricular fibrillation to heart failure it is essential that a normal cardiac mechanism be secured in as many cases as possible. We have already seen that both successful and unsuccessful cases for heterogeneous groups, that the only condition governing restoration of normal rhythm is the susceptibility of circus movement to the action of the drug. Theoretic considerations, therefore, impel us to employ quinidin impartially in all cases of auricular fibrillation. On the other hand, it must be understood, as Hewlett and Sweeney<sup>9</sup> have indicated, that any benefit derived from the use of quinidin is purely the result of a restored normal mechanism, an indirect effect of the drug. Before proceeding further, we must inquire into the nature of the drug's direct effect, and we find that quinidin is a muscle poison which exerts a distinctly depressant action on the myocardium. Whereas digitalis enjoys almost universal application in cardiac failure, the use of quinidin must be restricted not only to those cases of decompensation which have auricular fibrillation, but still further within that group. In every case we must decide as nearly as possible whether the benefit to be expected from resumption of normal rhythm will outweigh the harmful effect of quinidin as a muscle poison. In other words, we must form the best possible qualitative estimate of the extent to which disordered mechanism contributes to cardiac disability, if this is impossible, the only

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9 Hewlett and Sweeney J A M A 77 1793 (Dec 3) 1921

question remaining for decision before applying the quinidin test is the ability of the myocardium to withstand the temporary depressant action of the drug. Increasing experience with quinidin will help us to make these decisions. From these considerations it is obvious that every patient with cardiac dilatation or stasis of any degree should have the full benefit to his myocardium of digitalis before he is subjected to quinidin.

In order to test the effects of quinidin to the fullest extent, it has been my practice to employ it impartially in all cases of auricular fibrillation, exercising all possible precautions in view of the possible dangers of such procedure. Illustration of some of the points which I have discussed is furnished by one of our patients (Case 3) who had been under intermittent observation for a period of ten years, and was known to be exceptionally prone to acute dilatation of the heart. Slight emotional excitement was alone sufficient to bring on an attack. We were fully cognizant of the advanced state of his myocardial and endocardial involvement, and were convinced that auricular fibrillation was a relatively insignificant feature of his chronic cardiac decompensation. It was confidently predicted that the harmful effect of quinidin as a muscle poison would greatly outweigh any benefit which might be expected from resumption of normal rhythm. Quinidin therapy was three times interrupted by acute dilation of the heart. It cannot be said without qualification that quinidin was the sole cause of cardiectasis, for such an event had been observed numberless times, and was not more frequent or severe during quinidin administration than at other times. On the other hand, it is well to assume, if necessary, that quinidin was at least partially responsible. From this experience several conclusions may be drawn. In the first place, it is perfectly clear that the only important effect of quinidin in this patient was its depressant action on the myocardium. For this reason the experiment was necessarily terminated before any conclusions concerning the rôle of auricular fibrillation could be reached. Pursuing this point still further, however, it is possible that the actual means by which the direct depressant action of the drug was exhibited, rendering decompensation still worse, was the substitution of unaccustomed transition rhythms for an arrhythmia for which, during long sufferance, the myocardium had thoroughly compensated. Eyster and Fahr<sup>10</sup> have called attention to this possibility. There is little doubt that it represents an additional viewpoint from which the clinical use of quinidin must be regarded.

In many patients, however, compensation is not adversely affected by transition rhythms, even if the original arrhythmia is of long standing. As an extreme example, Case 7 may be cited. As far as compensation was concerned it made no apparent difference to this

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10 Eyster and Fahr Arch Int Med 29 59 (Jan) 1922



patient what his cardiac mechanism might be. On several occasions, while maintaining a normal mechanism under the influence of quinidin, he suddenly developed auricular flutter with immediate doubling or tripling of the ventricular rate. These and other changes occurred repeatedly without notice to the patient or modification of his condition. His subjective and objective signs seemed entirely independent of fibrillation, flutter, or normal rhythm. I have had opportunity to observe numerous other cases of similar character.

It remains for us to inquire into the results which may be ascribed to resumption of normal cardiac mechanism. In some cases no beneficial results are evident: either the patient is in worse condition because his myocardium reacted unfavorably to the depressant action of the drug, or to transition rhythms, or his state remains essentially unchanged. In Case 17, for instance, it was demonstrated that a normal rhythm made no perceptible difference in the patient's condition. It might have been possible, but certainly appeared unprofitable, to attempt to maintain the established sinus mechanism. A review of such cases strongly suggests that either auricular fibrillation may exist without in the least embarrassing the circulation, or that the myocardium, having compensated for the embarrassment incurred at the onset of auricular fibrillation, is now indifferent to any alteration in cardiodynamics which may be caused by arrhythmias of this character.

In a considerable number of patients, however, auricular fibrillation is a major factor for producing and maintaining myocardial decompensation, and these patients are tremendously benefitted by permanent restoration of their normal cardiac mechanism. A brilliant illustration is furnished by Case 14. After having been wholly incapacitated for a period of nine months by reason of myocardial incompetence, this patient was rapidly restored to his former vigor and was soon able to resume his duties as a street-car conductor. In perfect comfort he continues regularly at his work fifty or sixty hours a week, and feels that his health is as good as it ever was. His case may be summed up by saying that with auricular fibrillation he is a cardiac invalid, whereas with sinus rhythm he is a healthy man and an efficient economic unit.

Another illustration is recorded in Case 24. This patient had suffered from continuous auricular fibrillation and repeated attacks of severe cardiac decompensation for a period of five years, and his myocardium had never been able to compensate for the disordered mechanism. Although he was brought from a moribund state to a condition of relative comfort by means of digitalis and rest in bed, the last steps in attaining perfect compensation could not be accomplished by these measures. He still retained an annoying sense of precordial distress, and was still unable to lie flat in bed on account of air hunger.



Coincident with the resumption of normal rhythm all remaining symptoms disappeared promptly and completely, and the patient declared that he felt better than at any time in ten years. Under conditions such as these the tendency to recurrence of decompensation is greatly lessened, and the need for continuous digitalis therapy removed entirely.

One who has had opportunity to observe therapeutic successes of so impressive a character will be able to appreciate the great importance of a normal rhythm to numbers of our cardiac patients. Quinidin therapy has already been of such remarkable service in its peculiar field that to render it safe and generally applicable within that field calls for our most earnest efforts.

Brief reference may be made to the possibility of embolism subsequent to restoration of normal mechanism, to which attention has been called by Wilson and Herrmann, Ellis and Clark-Kennedy, Mackenzie, Orr and others. As Wilson and Herrmann<sup>11</sup> have indicated, patients with paroxysmal fibrillation are spontaneously subjected to the danger of embolism. In this connection, therefore, we may consider only the chronic fibrillators, in whom the danger is unquestionably a real one. On the other hand, are the cases of embolism from this cause more frequent than those which commonly occur in fibrillators who are being treated intensively with digitalis, or is it that we hear more of them by reason of the prominence of quinidin in medical literature? It is my belief that the actual percentage of such cases will be found almost equally divided between the two causes. We feel it our duty to extend the benefit of digitalis to our patients, although we realize fully the likelihood of subsequent embolism. Similarly, I believe we shall find it our duty to extend the benefit of a normal cardiac mechanism without probability of greater hazard.

#### CLINICAL REPORT

*Technic*—Quinidin sulphate was administered by mouth in all cases, to the first patient in solution, to all subsequent patients in gelatin capsules, sometimes with the lid of the capsule removed.<sup>12</sup> Approximately sixteen hours after the initial dose of 0.33 gm (5 grains), designed to test the possibility of idiosyncrasy to cinchona, the administration is usually begun with 0.33 gm four times a day. After a few days this amount is gradually increased if necessary. The largest twenty-four hour dosage was 3.33 gm (50 grains), and the largest total dosage was 36.0 gm (545 grains) over a period of twenty days with one intermission of two days (Case 25). Each patient has been

11 Wilson and Herrmann. J. A. M. A. 78:865 (March 25) 1922.

12 It is worthy of note that Boden<sup>2</sup> has ventured to employ the drug intravenously in doses as high as 0.4 gm (6 grains). He reports no untoward results from this procedure.

hospitalized for the first course of treatment, but not, as a rule, for subsequent therapy. In view of the known tendency of auricular fibrillation to recur, continuous treatment with quinidin following resumption of normal rhythm is, of course, essential, just as continuous digitalis therapy has been essential in auricular fibrillation. For this purpose the smallest effective dosage is used. It is a curious fact that many workers have expected the sinus mechanism, once restored, to continue indefinitely without support, and have regarded a relapse to fibrillation under these conditions as evidence that treatment with quinidin is a failure. It is to be emphasized that the only important consideration in quinidin therapy is to observe the effect of normal rhythm on compensation over the longest possible period of time.

Unpleasant symptoms attributable to quinidin have been inconspicuous. There were a few instances of headache, tinnitus, fleeting visual disturbance, restlessness, nausea and vomiting, but nothing of an alarming nature appeared except as described in Case 3.

Thirty-six patients have received one or more courses of quinidin. One of these (Case 20) was not a case of auricular fibrillation, three left the hospital before the treatment had been completed. Of the remaining thirty-two cases, twenty (62 per cent) responded with a normal mechanism. It has been impossible to follow carefully the subsequent course of events in all cases, but it is fairly certain that permanent benefit has been secured in fifteen cases, which is 47 per cent of the entire series and 75 per cent of the restored cases.

*Electrocardiograms*—These are analyzed in the accompanying table. It will be noted that in several cases the  $P$ - $R$  interval exceeds the upper limit of normal, but to assume from this that quinidin depresses  $A$ - $V$  conduction is obviously unjustifiable for the reason that we have no means of knowing the original  $P$ - $R$  interval. Furthermore, such an assumption means a disproportionately great depression of  $A$ - $V$  conduction in contrast with other effects, for disturbance of intra-auricular conduction occurred but once and the recorded changes in  $QRS$  interval are negligible. That prolongation of the  $P$ - $R$  interval is extremely unlikely under clinical conditions is apparent from a consideration of the experimental results reported in my preceding paper. Moreover, I have knowledge of one case in which a very long  $P$ - $R$  interval appeared after the abolition of fibrillation, but reference to a control record, made some time before the original onset of the patient's disordered mechanism, showed this long interval to be the natural one for the patient. The average  $P$ - $R$  time for the twenty patients is 0.183 second, which might well be the average for a like number of normal hearts.

## ANALYSIS OF ELECTROCARDIOGRAMS

Case No	P-R Time Maximum (Seconds)	QRS Time Maximum (Seconds)	Character of P-wave	Character of T wave	Voltage of QRS + Increase — Decrease	Remarks
1	0 22	No change	Notching and semi-inversion in Leads II and III	No change	No change	
4	0 16	No change	No change	No change	No change	
5	0 215	Increased by 0 03	Notching in Lead I	Invert to upright in Lead III	— Leads II and III	
6	0 162	No change	No change	No change	+ Lead III	Change from bizarre QRS to notched R, Lead III
7	0 22	No change	No change	No change	+ all leads	
9	0 22	Increased by 0 02	No change	No change	+ all leads	
11	0 21	No change	Diphasic in Lead III	No change	No change	
14	0 20	No change	Notching in Leads I and II, invert and variable in Lead III	No change	— Lead III	Intra-auricular block
16	0 22	No change	No change	No change	+ all leads	S wave appears in Lead I, character of QRS changed in Leads II and III
17	0 24	No change	Slight notching in Lead II	No change	No change	
18	0 12	Increased by 0 03	Isoelectric in Lead I, invert in Leads II and III	No change	+ all leads	
20	No change	Increased by 0 02	No change	Greatly reduced voltage in Leads II and III	+ Lead II	
21	0 12	No change	No change	No change	+ all leads	
24	0 16	No change	Notched in Leads I and II, diphasic in Lead III	No change	+ all leads	
25	0 18	Increased by 0 02	Isoelectric in Lead I, diphasic in Lead III	Voltage initially reduced, later recovering	No change	
28	0 16	No change	Diphasic in Lead III	No change	No change	
29	0 20	No change	Notched in Lead I, invert in Lead III	No change	No change	
30	0 18	No change	Notched in Leads I and II, diphasic in Lead III	No change	+ all leads	S wave substituted for R-wave in Lead I
31	0 152	No change	No change	No change	— all leads	
33	0 16	No change	Notched in Lead I, diphasic in Lead III	No change	+ Leads I and III	
35	0 17	No change	Notched in Lead I	No change	— Lead I	

Although notching and semi-inversion of the P wave seem extraordinarily common, deductions therefrom are open to the same criticism as those concerning the *P-R* interval. However, one is probably justified in the belief that the frequent changes in direction and sign of the *P* wave, often conspicuous from beat to beat, which take place for a time after resumption of normal rhythm, are due to instability in location of the pacemaker. Changes in voltage of the initial phases of the ventricular electrocardiogram, occasionally associated with minor alterations in the character of the individual waves, is rather common, but no explanation is forthcoming.

The production by quinidin of undoubted pure auricular flutter at extremely low rates, reaching 130 per minute in one of my patients (Case 8, Fig 16), is one of the most interesting features from the standpoint of rhythm. It is necessary to revise the old dictum that flutter is unlikely at rates slower than 200 per minute.

#### PROTOCOLS

Detailed reports of seven successful and six unsuccessful cases from our series are given.

CASE 1 (84011) —A B, woman, aged 50, had noticed no symptoms of heart disease until March 8, 1921, when she was subjected to a severe fright. Immediately she became conscious of palpitation, tachycardia, and air hunger. Her symptoms progressively increased, and when examined, April 15, she was found to have primary myocardial disease, moderately decompensated, and auricular fibrillation. There was no arterial hypertonus. Patient improved under digitalis, and was not seen again until May 20, 1921, when decompensation was found to have returned. After the physiologic effect of digitalis had been secured, quinidin sulphate, in solution, was given as follows: May 23, 1 gm (15 grains), May 24, 0.33 gm (5 grains), May 25, 1.33 gm (20 grains), May 26, 0.67 gm (10 grains), total, 3.33 gm (50 grains), patient vomited some of the drug, so that the exact amount retained is unknown. Normal mechanism became established May 26, and was followed by great improvement in subjective symptoms and possibly lessened cardiacetasis. Auricular fibrillation has not recurred and compensation is being well maintained.

CASE 2 (6) (85869) —C T, man, aged 50, had suffered from air hunger on exertion for ten months. At 36 he had passed through an attack of scarlet fever. Clinically, the picture was that of primary myocardial disease with slight enlargement of both right and left ventricles, and auricular fibrillation. There was no evidence of stasis, hence digitalis was omitted and quinidin therapy immediately instituted as follows: August 4, 1.33 gm (20 grains), August 5, 1.33 gm (20 grains), August 6, 2.67 gm (40 grains), total, 5.33 gm (80 grains). While the patient was in the act of palpating his radial pulse the evening of August 6, he noted a short period of very rapid rate, suddenly interrupted by a change to slow, regular beating, which continued without further incident. Following the resumption of normal mechanism, the symptoms were wholly alleviated, and the patient was able to continue an active life in perfect comfort, without therapy, for nearly five months. Auricular fibrillation reappeared, Jan 26, 1922, accompanied by considerable discomfort, and was again abolished by a total dosage of 3.67 gm (55 grains) of quinidin sulphate. The clinical result was as brilliant as on the former occasion.

CASE 3 (7) (85848) —G S, man, aged 43, had been incapacitated since 1917 because of air hunger, weakness, edema and ascites. In April, 1920, ten liters

of fluid had been removed from the peritoneal cavity, and there had been many subsequent taps. In September, 1920, the patient was found to be severely decompensated, with extensive cardiac enlargement, auricular fibrillation, tremendous ascites, swollen liver, bilateral hydrothorax, and dependent edema. Rest and thorough digitalization restored good compensation. In August, 1921, the patient presented himself in a condition almost identical with that of the previous year. Rest and digitalis were again effective in restoring compensation. Patient was relieved of 30 pounds of edema and became very comfortable. Physical examination showed extensive symmetrical cardiac hypertrophy, auricular fibrillation, and atrophic cirrhosis of the liver. Synechia cordis was considered a chief factor in the myocardial disease. The blood Wassermann was negative. Quinidin sulphate was given as follows: August 10, 1.33 gm (20 grains); August 11, 0.33 gm (5 grains), total, 1.66 gm (25 grains). Normal rhythm became established August 11, immediately following a pulsus bigeminus of unknown origin. The unstable character of the patient's cardiac mechanism was soon revealed. August 19, three days after discharge from the hospital, auricular fibrillation had returned. Five days later, after 3.33 gm quinidin had been given, normal rhythm was found to be restored. Thereafter a daily dose of 0.67 gm was given until September 7. August 31 found the

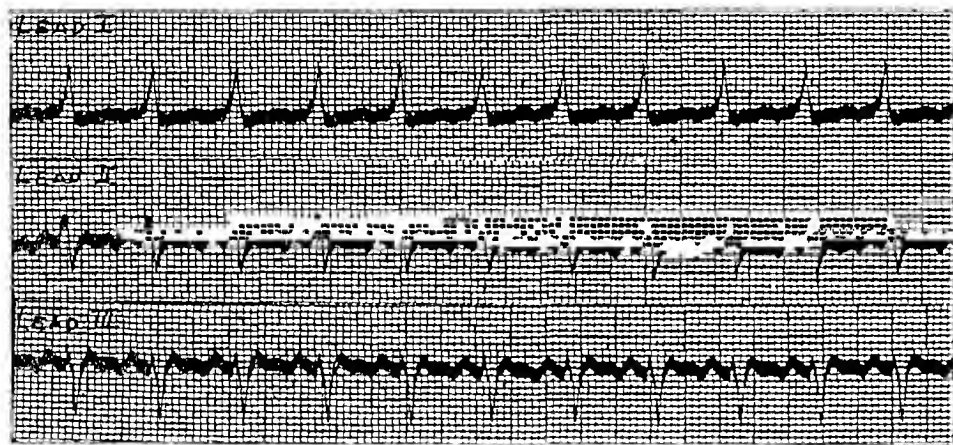


Fig 4—Electrocardiogram of Case 3 (7) Pure auricular flutter. Auricular rate 250, ventricular rate, 125, per minute.

patient with a normal mechanism, but September 7 an electrocardiogram showed pure auricular flutter (Fig 4). Quinidin was withdrawn, and two days later fibrillation had returned. Tincture of digitalis was then begun and continued uninterruptedly until September 30, when normal rhythm and digitalis coupling appeared simultaneously (Fig 5). All medication was then discontinued. Examination October 7 and 14 showed uncomplicated normal rhythm. Similar changes in rhythm were repeated many times in the ensuing months. Although a daily ration of from 1 to 1.33 gm quinidin might have sufficed to preserve normal mechanism indefinitely, it became apparent that myocardial compensation was entirely independent of rhythms.

CASE 4 (14) (83579)—C M, male, aged 52, suffered severely from acute articular rheumatism at 14, and again at 21, at which time the first symptoms referable to heart disease made their appearance. Aside from slight shortness of breath on exertion, however, the patient remained in good condition until early in 1921, when he became seriously decompensated. Thereafter, he was never free from air hunger, weakness, edema and ascites. He presented the clinical picture of mitral regurgitation, with moderate enlargement, predominantly of the left ventricle, and auricular fibrillation. The latter was known positively since March 25, 1921, but the patient declared that his pulse had been constantly "uneven" for at least ten years. On several occasions rest and digitalis restored a considerable degree of compensation, but he failed to

regain his former comfort and capacity. Finally, after thorough digitalization, quinidin sulphate was given as follows: October 26, 1 gm (15 grains), October 27, 2 gm (30 grains), October 28, 2 gm (30 grains), October 29, 2.33 gm (35 grains), October 30, 2.67 gm (40 grains), October 31, 1.33 gm (20 grains), total, 11.33 gm (170 grains). Normal mechanism appeared October 31, complicated at first by intra-auricular block<sup>13</sup> and by auricular premature beats. The change to sequential rhythm was signalized by remarkable improvement in the patient's condition, the details of which have already been described. Small doses of quinidin (0.33 gm in from twenty-four to forty-eight hours) were continued from November 9 to December 21, then omitted. Patient's condition remained unchanged until Jan 30, 1922, when suddenly the former indefinable uneasiness and lessened capacity returned by reason of reversion to auricular fibrillation. A small amount of quinidin (1 gm) immediately restored normal rhythm, and, thereby, adequate minute-volume flow of blood. The discomfort disappeared at once and the patient resumed his activities. Since that time he has regularly taken 0.33 gm quinidin on alternate days, in consequence of which normal mechanism and compensation are perfectly maintained.

CASE 5 (17) (87473)—E. H., female, aged 51, weighing 250 pounds, had shown symptoms of myocardial incompetence for three years. She complained of shortness of breath, palpitation, headache, dizziness and slight edema of the ankles. Although the symptoms had gradually increased in severity, there had been no complete cardiac failure. Patient was found to be suffering from severe arterial hypertonus (240/140), chronic myocardial disease with auricular fibrillation and failing compensation, and chronic interstitial nephritis. After considerable improvement had resulted from measures designed to reduce the arterial hypertonus, quinidin sulphate was given as follows:

From November 18 to November 26, 13.00 gm (195 grains)

From November 29 to December 5, 8.33 gm (125 grains)

Normal rhythm became established November 26, but soon gave way again to auricular fibrillation which the second course of quinidin failed to abolish. It was determined from subsequent observation that sequential mechanism contributed nothing toward betterment of the patient's condition.

CASE 6 (24) (88337)—F. F., a man, aged 65, began to have palpitation and edema in June, 1916. His condition gradually grew worse, and in January, 1917, he was admitted to the hospital in a state of moderate decompensation. He presented the picture of primary myocardial disease with auricular fibrillation, and chronic nephritis. There was extensive enlargement of both right and left ventricles and right auricle. Blood pressure was 135/85. After a month's treatment he was well compensated, and underwent a herniorrhaphy before leaving the hospital. The next cardiac breakdown occurred in 1919, when he spent four months in the Cleveland City Hospital and again recovered good myocardial function. His third experience of heart failure began in 1921, culminating in January, 1922, in his admission to the hospital in a condition of the most extreme myocardial decompensation. Once again there was a prompt response to rest and digitalis, but orthopnea and slight precordial anxiety persisted.

Patient was treated at Lakeside Hospital in December, 1902, for lead poisoning. There was no evidence of heart disease at that time. Although the patient numbers typhoid fever and pneumonia among his past illnesses, and admits that he has been intensively treated for syphilis on several occasions, it is probable that his myocardial disease did not originate from these sources. Auricular fibrillation has persisted for five years. Quinidin sulphate was given as follows: January 20, 0.33 gm (5 grains), January 21, 0.67 gm (10 grains), January 22, 1 gm (15 grains), January 23, 0.33 gm (5 grains), total, 2.33 gm (35 grains). Normal rhythm appeared January 22, after 2 gm had been given. Almost immediately the persisting precordial anxiety and orthopnea vanished, leaving

the patient in perfect comfort. It was soon discovered that a daily dose of 1 gm was the amount required to prevent return of fibrillation. This dosage has been continued for several months with entirely satisfactory results.

CASE 7 (25) (88484) —M C, a man, aged 52, had been perfectly well until late in December, 1921, when he was suddenly seized with precordial pain and extreme air hunger. The symptoms were so severe that the patient was at once incapacitated. The etiology of his heart disease could not be determined from the history. He was found to have chronic myocardial disease with mitral stenosis and auricular fibrillation. There was no demonstrable stasis. The sudden onset of his trouble was interpreted as the result of the initial appearance of auricular fibrillation. Quinidin therapy was carried out as follows:

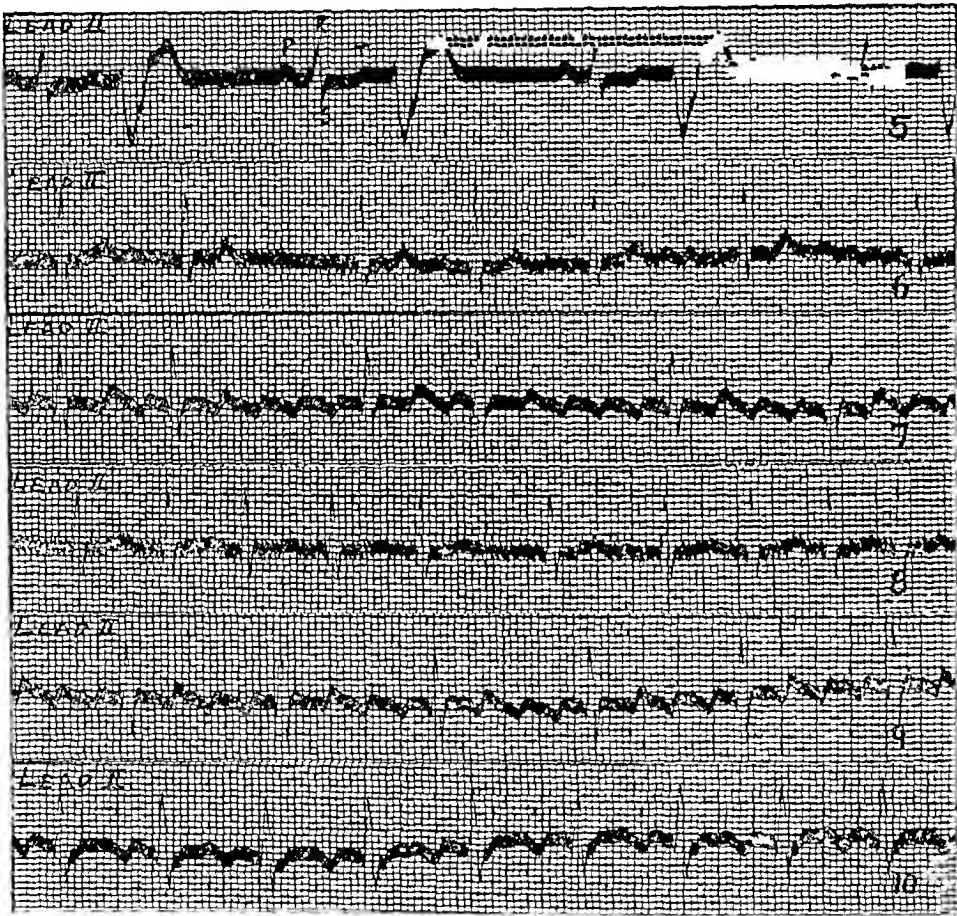


Fig 5—Case 3 (7) Electrocardiogram made after digitalization

Fig 6—Electrocardiogram of Case 7 (25) showing auricular fibrillation

Fig 7—Electrocardiogram of Case 7 showing pure auricular flutter. Auricular rate 272 per minute. Ventricle arrhythmic.

Fig 8—Electrocardiogram of Case 7 showing auricular fibrillation

Fig 9—Electrocardiogram of Case 7 showing pure auricular flutter. Auricular rate 272, ventricular rate 68, per minute.

Fig 10—Electrocardiogram of Case 7 showing pure auricular flutter. Auricular rate 206, ventricular rate 103, per minute.

January 16, auricular fibrillation (Fig 6), January 23, 1.00 gm (15 grains), January 24, 1.33 gm (20 grains), January 25, 1.67 gm (25 grains), January 26, 1.67 gm (25 grains), pure auricular flutter (Fig 7), January 27, 1.33 gm (20 grains), auricular fibrillation (Fig 8), January 28, 2.00 gm (30 grains), January 29, 2.00 gm (30 grains), January 30, 2.67 gm (40 grains), pure auric-



ular flutter (Fig 9), January 31, 2.67 gm (40 grains), February 1, 2.67 gm (40 grains), pure auricular flutter (Fig 10), February 2, 2.00 gm (30 grains), impure auricular flutter, February 3, auricular fibrillation, February 6, 0.67 gm (10 grains), February 7, 2.67 gm (40 grains), February 8, 3.33 gm (50 grains), February 9, 3.33 gm (50 grains), February 10, 3.33 gm (50 grains), normal mechanism (Fig 11), total, 36.34 gm (545 grains). The entire medication was carried through without incident. In the ensuing three months small doses (0.33 gm in from twenty-four to forty-eight hours) have sufficed to maintain normal rhythm. Patient's compensation is constantly good, and he has been able to do light work.

CASE 8 (2) (85017)—E S, a woman, aged 63, had suffered from steadily progressing edema and shortness of breath since January, 1921. In June she was found to be in a condition of severe decompensation, with extensive edema, ascites and air hunger. The clinical picture was that of chronic nephritis, arteriosclerosis of the Gull and Sutton type, chronic myocardial disease and auricular fibrillation. There was considerable enlargement of the right and left ventricles, predominantly the left. Blood pressure was 180/110. After a marked improvement had been effected by means of rest and digitalis, quinidin

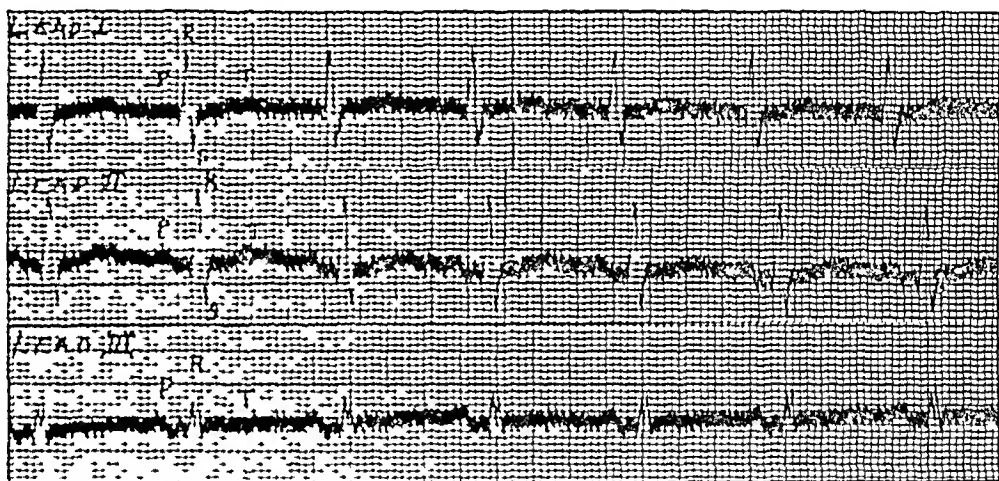


Fig 11—Electrocardiogram of Case 7 showing normal mechanism

was given as follows: June 22, 2.00 gm (30 grains), June 23, 2.00 gm (30 grains), July 1, 2.00 gm (30 grains), July 2, 0.67 gm (10 grains), July 13, 1.33 gm (20 grains), July 14, 1.33 gm (20 grains), July 15, 1.33 gm (20 grains), July 25, 2.00 gm (30 grains), July 26, 2.00 gm (30 grains), July 27, 2.00 gm (30 grains), July 28, 2.00 gm (30 grains), July 29, 2.00 gm (30 grains), July 30, 1.00 gm (15 grains), total 21.66 gm (325 grains). The first suspicion that compensation was being unfavorably affected by quinidin was ultimately disproved. During the last course, at the end of which 11 gm (165 grains) had been taken, there were no untoward symptoms. No change in mechanism was effected.

CASE 9 (3) (82549)—J K, a man, aged 41, was suffering from very severe rheumatic endocarditis and myocarditis which had been steadily progressing for thirty years. In May, 1921, he had tremendous cardiac enlargement, very severe stenosis and insufficiency of both the aortic and mitral valves, and chronic auricular fibrillation. The disordered mechanism was a matter of hospital record in 1911. Reference has already been made to the frequency of acute dilatation of the heart in this case. At the time when quinidin therapy was begun the myocardium was in a relatively good state of compensation, that is, the patient was free from edema, there was no demonstrable stasis, and he was perfectly comfortable as long as he remained at rest in bed. May 25, 1.00 gm (15 grains), May 26, 1.67 gm (25 grains). Acute dilatation



of the heart occurred May 26, with the help of strophanthin the usual good recovery was made. To comply with the patient's desire, a second attempt was made June 10, 1.00 gm (15 grains). This was in turn followed by acute dilatation with good recovery. Finally, at the urgent insistence of the patient, a third course was started. A daily dose of 0.67 gm (10 grains) was given from August 22 to September 1, inclusive. It was then discontinued for no other reason than severe tinnitus, later being resumed as follows: September 5, 0.33 gm (5 grains), September 6, 0.67 gm (10 grains), September 7, 0.67 gm (10 grains), September 8, 0.67 gm (10 grains), September 9, 1.00 gm (15 grains), September 10, 0.67 gm (10 grains), September 12, 0.33 gm (5 grains), September 13, 0.33 gm (5 grains), total, 4.67 gm (70 grains).

Acute dilatation here made its third appearance, and was again recovered from without serious difficulty. No more quinidin was administered at any time. Patient died more than three months later from acute myocardial failure.

CASE 10 (8) (85833)—M R, a woman, aged 41, was found to be suffering from subacute myocarditis with failing compensation. Her symptoms, which dated from 1917, had become greatly aggravated following an attack of pneumonia in January, 1921. Edema first appeared in July, 1921. Physical examination revealed symmetrical cardiac enlargement of moderate extent, auricular fibrillation (Fig 12), bilateral hydrothorax, ascites, and dependent edema. Patient was very weak and short of breath. While under observation in the

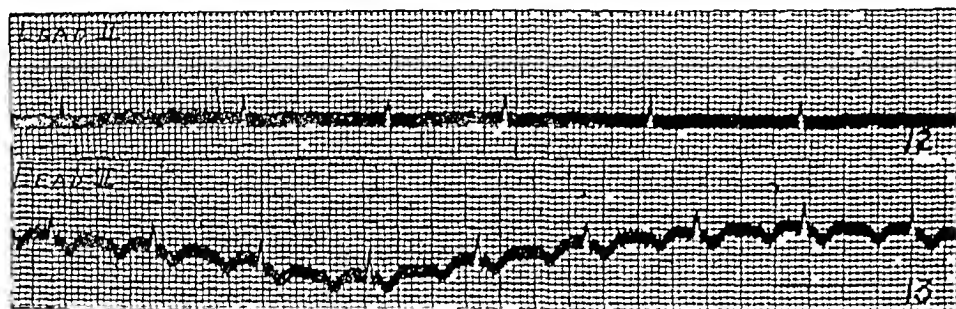


Fig 12—Electrocardiogram of Case 10 (8) showing auricular fibrillation

Fig 13—Electrocardiogram of Case 10 (8) showing pure auricular flutter  
Auricular rate 186, ventricular rate 93 per minute

hospital she developed mitral stenosis. Quinidin was started while some fluid still remained within the pleural and peritoneal cavities. August 6, 1.00 gm (15 grains), August 7, 1.33 gm (20 grains), August 8, 0.67 gm (10 grains), August 9, 1.33 gm (20 grains), August 10, 1.33 gm (20 grains), August 11, 2.00 gm (30 grains), August 12, 0.67 gm (10 grains), total, 8.33 gm (125 grains). Throughout this period compensation certainly did not improve, nor did it become appreciably worse, and there was no change in mechanism. The second trial of quinidin was made after compensation had been well established. August 28, 1.33 gm (20 grains), August 29, 1.33 gm (20 grains), August 30, 1.33 gm (20 grains), August 31, 1.33 gm (20 grains), September 1, 0.67 gm (10 grains), September 2, 0.67 gm (10 grains), September 3, 0.67 gm (10 grains), total, 7.33 gm (110 grains). August 31, after 4 gm, the pulse for the first time became regular and rhythmical, but remained fast. An electrocardiogram showed pure auricular flutter (Fig 13). Massive doses of tincture of digitalis failed to cause reversion to fibrillation. Auricular flutter persisted thereafter for six months, during which time compensation was well supported and the patient comfortable so long as a high degree of A-V block was maintained by means of digitalis.

In March, 1922, an effort to carry the mechanism through flutter to normal rhythm was made. March 4, pure auricular flutter (Fig 14), March 11, 0.67 gm (10 grains), March 12, 1.33 gm (20 grains), March 13, 1.33 gm (20

grams), pure auricular flutter (Fig 15), March 14, 133 gm (20 grains), March 15, 167 gm (25 grains), March 16, 200 gm (30 grains), March 17, 233 gm (35 grains), March 18, 267 gm (40 grains), March 19, 267 gm (40 grains), March 20, 133 gm (20 grains), March 21, pure auricular flutter (Fig 16), total, 1733 gm (260 grains) March 23, 267 gm (40 grains), March 24, 267 gm (40 grains), March 31, 067 gm (10 grains), April 1, 267 gm (40 grains), April 2, 267 gm (40 grains), April 3, 200 gm (30 grains), total, 1335 gm (200 grains) On several occasions the rate of flutter was driven very low, but each time, at the critical point, medication had to be discontinued because of tinnitus, fleeting visual disturbances, nausea and vomiting Permanent auricular flutter seems to be the final result in this patient, but her condition is no worse than it was with fibrillation

CASE 11 (19) (87641)—T N, a man, aged 49, began to have symptoms of myocardial weakness in 1914, since which time he had never been free from an

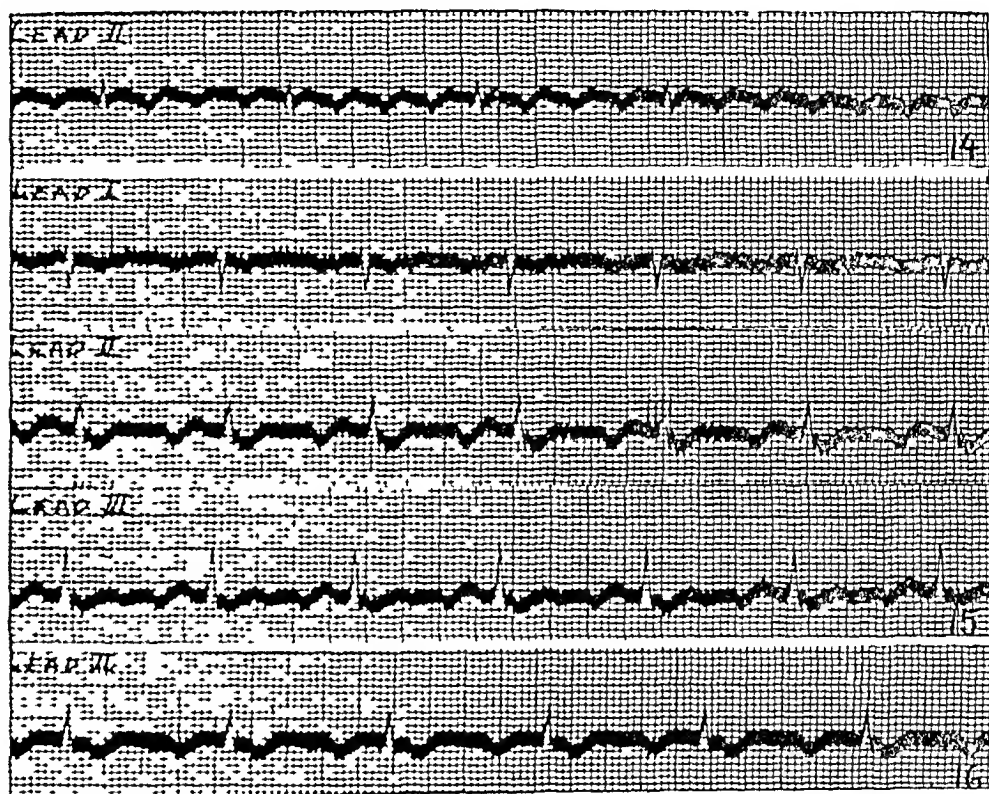


Fig 14 — Electrocardiogram of Case 10 showing pure auricular flutter Auricular rate 230 per minute Ventricle arrhythmic

Fig 15 — Electrocardiogram of Case 10 showing pure auricular flutter Auricular rate 150, ventricular rate 75, per minute

Fig 16 — Electrocardiogram of Case 10 showing pure auricular flutter Auricular rate 130, ventricular rate 65, per minute

hunger, weakness and edema He had accomplished only seventeen months' work in seven years The clinical picture was that of severe synecchia cordis, and mitral stenosis of rheumatic origin There was considerable enlargement of both right and left ventricles, and right auricle, and a very large, vigorously pulsating liver Blood pressure was 110/70 After compensation had become well established quinidin was given in the endeavor to restore normal rhythm A total amount of 16 gm (240 grains) was administered over a period of eight days, without intermission, the maximum daily dose being 267 gm (40 grains) The disordered mechanism was not abolished, and there was no evidence that compensation had been modified in any way

CASE 12 (22) (87471) —G N, a man, aged 55, had suffered since 1917, from shortness of breath on exertion and pain in the epigastrium. He had spent much time in hospitals on account of myocardial failure. Physical examination in December, 1921, revealed moderate decompensation with slight dependent edema and left hydrothorax. There was some enlargement of both the right and left ventricles, and right auricle, general arteriosclerosis and auricular fibrillation. Records show that the fibrillation was present in February, 1919. Blood pressure was 130/80. After thorough digitalization, quinidin was given as follows: January 3, 0.33 gm (5 grains), January 4, 0.067 gm (10 grains), January 5, 1.33 gm (20 grains), January 6, 1.33 gm (20 grains), January 7, 1.67 gm (25 grains), January 8, 2.00 gm (30 grains), January 9, 3.00 gm (45 grains), January 10, 2.67 gm (40 grains), January 11, 2.67 gm (40 grains), January 12, 1.33 gm (20 grains), total, 17.00 gm (255 grains).

There was no change in mechanism, and no modification of compensation.

CASE 13 (27) (88173) —G M, a man, aged 65, began to notice unwonted air hunger and weakness in January, 1920. These symptoms grew gradually worse, and several months later edema of the ankles made its appearance. Patient was admitted to the hospital Oct 25, 1920, in a state of decompensation, with extensive edema and ascites. He presented the picture of chronic interstitial nephritis, chronic myocarditis, and auricular fibrillation. Blood pressure was 180/110. He was discharged Nov 30, 1920, in a greatly improved condition, and remained fairly well until September, 1921, when the former symptoms returned with renewed intensity. He was readmitted to the hospital Dec 30, 1921. Prior to admission he had been taking digitalis in sufficient amount to cause characteristic slow bigemini pulse. In spite of the strong digitalis effect, he had tremendous edema and ascites, swollen liver, and extensive dilatation of the heart. Feb 1, 1922, all retained body fluid had been eliminated and compensation satisfactorily reestablished. Quinidin sulphate was given as follows: February 6, 0.33 gm (5 grains), February 7, 1.33 gm (20 grains), February 8, 2.00 gm (30 grains), February 9, 2.00 gm (30 grains), February 10, 2.00 gm (30 grains), February 11, 1.00 gm (15 grains) total 8.67 gm (130 grains). The auricular fibrillation was not abolished, but February 10, after 6 gm of the drug had been taken the electrocardiogram showed left bundle branch block.<sup>14</sup> Quinidin was withdrawn, and February 13 the branch lesion had completely disappeared.<sup>14</sup>

#### SUMMARY AND CONCLUSIONS

1 The result attained by the use of quinidin in a case of ventricular paroxysmal tachycardia is described. The manner in which the drug acts in cases of this character is discussed.

2 Clinical evidence is presented which lends support to the theory that the action of quinidin in abolishing circus movement is not conditioned by the type of cardiac lesion, degree of decompensation, duration of fibrillation, etc., but is essentially related to the pathologic physiology of the auricular muscle.

3 The most important contribution of quinidin to clinical cardiology is that it provides a means by which the rôle of auricular fibrillation in myocardial failure may be quantitatively estimated.

4 Quinidin is universally a heart muscle poison. In each patient an estimate of this effect must be carefully weighed against the expec-

14 This issue, page 32, Figure 46

tation of benefit to be derived from restoration of normal sinus mechanism. Indications for the use of digitalis and quinidin are entirely separate and clearly defined.

5 The effect of restored normal cardiac mechanism on compensation is illustrated by presentation of cases.

6 Electrocardiograms made before and after resumption of normal rhythm are analyzed.

# ON THE TECHNIC OF THE DETERMINATION OF THE VELOCITY OF THE ARTERIAL PULSE WAVE <sup>†</sup>

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As early as the third century B C, there was a conception in Greek medicine (Erasistratus) that the pulse in the parts of the body nearest the heart appeared earlier than at the extremities. This conception seems to have been forgotten until 1734, when it was emphasized again by Weitbrecht <sup>1</sup>. The first to measure the time difference in the appearance of the pulse in the central and the more peripheral arteries was E H Weber, <sup>2</sup> in 1850. Weber used palpation of the pulse, and took the time on an ordinary watch. He found by this means that the pulse wave in the dorsal artery of the foot appeared later than the pulse wave in the external maxillary artery. A few years after that, Vierordt, <sup>3</sup> in Germany, and Marey, <sup>4</sup> in France, introduced the sphygmograph. In 1861, Buisson <sup>5</sup> did the first determinations of the velocity of the pulse wave by means of a graphic method. He used two Marey tambours, one was applied to the proximal part of an artery, and the other to a more peripheral part. The motions caused by the pulse wave were conducted by means of air to two other tambours, to which small levers were attached. The movements of these levers were registered on smoked paper on the same rotating cylinder. The following methods, including ours, can be considered as developments of the Buisson principle, they differ in respect to the manner in which the movements of the arterial wall are transmitted, and in respect to the manner in which these movements are recorded.

After having tried different methods, Czermak, <sup>6</sup> in 1864, devised a method, which, in its main features, was the same as Buisson's. In 1872, Landois <sup>7</sup> transferred the movements of the pulse to the smoked paper by means of electromagnets. Grummach, <sup>8</sup> in 1879, tried Landois'

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\* From the Medical Clinic of the University of Copenhagen

1 Weitbrecht, J. (Cited from Landois) *Comm acad imper scient Petropol* 1734-1735, p 317

2 Weber, E H. *Berichte über die Verhandl Königl Sach, Geschellsch d Wissensch Math-phys, Classe* 1850 3 196, 1851

3 Vierordt, K. *Die Lehre vom Arterienpuls in gesunden und kranken Zuständen gegründet auf einer neuen Methode der bildlichen Darstellung des menschlichen Pulses*, Braunschweig, 1855, p 56

4 Marey. *Recherches sur le pouls au moyen d'un nouvel appareil enregistreur—le sphygmographe*, Paris, 1860

5 Buisson, P C. *Gaz méd* 20 319, 1861

6 Czermak, Y N. *Prager med Wchnschr*, No 17, 1864 (cited after Landois)

7 Landois, L. *Die Lehre vom Arterienpuls* Berlin, p 294, 1872

8 Grummach, E. *Arch f Anat u Physiol (Physiol Abteil)*, p 416, 1879

method, but found that it had too many possibilities of error, and he himself devised a method, which in its main features corresponded to Buisson's, but in which an improved method of time marking was employed. The Buisson-Grummach method became the standard method used in studies of the velocity of the pulse rate in the following period. It seems easy, but it has, however, several difficulties, particularly in the adjustment of the levers to the smoked paper. If they are too tight, the movements are hampered, and if they are not tight enough, the recording of the movements is unsatisfactory. It is furthermore necessary to have the points of the levers in perpendicular lines (one above the other), if they are not, it is necessary to determine the horizontal distance between them, which is not always possible. Ruschke<sup>9</sup> tried to avoid these difficulties by a photographic record of the movements of the levers. His method is rather difficult to use, because it requires that the work be done in the dark.

An extensive historical review of the technic has been made lately by Laubry, Mougeot, and Giroux<sup>10</sup>. These investigators themselves use the Buisson-Grummach method. In 1920-1921 the hot wire apparatus was introduced into medicine (Tucker,<sup>11</sup> Hill<sup>12</sup>) for registration of pulse and heart beat and of movements of similar kind. The oscillations of a string which is a part of a Wheatstone bridge, are recorded on an electrocardiograph. It moves when it is cooled from the puff of air caused by the movement of the skin over the vessel. The stream of air is conducted through a rubber tube. In 1921 it was applied by Hill<sup>13</sup> to a determination of the velocity of the pulse wave, and in 1922 Bramwell and Hill<sup>14</sup> published a few determinations on patients. By this method extremely beautiful curves of the pulse are obtained. We think, however, that the usual transmission by means of rubber tubes and tambours is more practical for ordinary clinical purposes than the very ingenious hot wire method, and it does not seem to be less accurate if the rubber tubes are of equal lengths and the tambours equally moveable.

It had also occurred to us,<sup>15</sup> in attempting to study the velocity of the arterial pulse wave, that the camera of the electrocardiograph might

9 Ruschke, K. Beitrag zur Lehre von der Fortpflanzungsgeschwindigkeit der Pulswellen bei gesunden und kranken Individuen, Dissert., Jena, 1912.

10 Laubry, Ch. Mougeot, A., and Giroux, R. Arch d mal du coeur **2** 49, 1921.

11 Tucker, W. S., and Paris, E. T. Phil Tr Roy Soc London **221** 389, 1921.

12 Hill, A. V. Lancet **2** 752, 919, 1921, J Physiol **54** 53, 1920.

13 Hill, A. V. J Physiol **54** 119, 1921.

14 Bramwell, J. C., and Hill, A. V. Lancet **2** 891, 1922.

15 A preliminary report of our procedure has been given in the Danish Society for Internal Medicine, April, 1921, and in Compt rend Soc de biol **84** 371, 1921.

be employed to record the curve obtained from the arteries. The use of this apparatus made it possible, at the same time, to inscribe the electrocardiogram.

The procedure adopted is as follows. Two arterial pelotes are applied as usual, one to the carotid, and one to the radial artery. Two rubber tubes of equal length transmit the movements of these pelotes by air to two tambours, so placed on an appropriate support, that the recording levers are from 20 to 30 cm. from the narrow slit of the camera of the electrocardiograph, between it and the light system. The time is recorded in the manner usual in taking electrocardiograms. As the slit is very narrow, the parts of the levers which are recorded, are always focussed to points which lie on the same ordinate, that is to say, on a line perpendicular to the direction of movement of the photographic plate, and parallel to the time lines. In this way the difficulties involved in using smoked paper are avoided, as well as the very considerable inconvenience of working in the dark, as is done in the Ruschke method.

As a matter of fact, the electrocardiograph is not indispensable. Any camera, in which the sensitive surface moves at a uniform and sufficiently rapid rate, a chronograph and a light source of great intensity with a system of lenses for projecting the light on the slot of the photographic chamber, for instance Frank's kymographion,<sup>16</sup> will answer the purpose. The electrocardiograph is preferable, however, when it is available, because it makes it possible to record the electrocardiogram at the same time as the two arterial curves. This arrangement has the advantage of indicating to what heart contraction a given pulse wave corresponds, a very useful correlation in the study of the velocity of arterial waves in patients presenting various forms of arrhythmia, and on the much discussed subject of the velocity of the large and small arterial waves, as in *pulsus altermans*, and in *pulsus bigeminus* of extrasystolic origin. The photographic plate, or film, must move with a speed two to three times that employed for recording electrocardiograms.<sup>17</sup> The foot points of the arterial waves must be clearly defined. This is a point which is not always obtained by using ordinary pelotes. The pelote which is placed over the radial artery is of the spring variety used by Mackenzie. It is fastened on the cross piece which connects two pieces of wood. To prevent this support from slipping, there are fastened to the under surface of the parallel pieces of wood, strips of rubber which are triangular in cross section. In the free space between these, the knob of the pelote falls.

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16 Frank, O. *Technik u. Methodik*, Ztschr. f. biol. **1** 105, 1908.

17 More often it is well to use a speed of 4 meters per minute.

The carotid receiver (Fig 1) is an ordinary metal tambour. To the center of the rubber membrane is fastened a small metal knob to be applied to the artery<sup>18</sup>. This tambour has a rather long shank. This portion of the apparatus rides inside a cylinder, the shank of the tambour passing through an opening at the upper end. A slot is cut in one side of the cylinder, through which passes a thread rod from the tambour. The nut on that rod serves to fasten the tambour in position. There is a spring on the shank which presses the head of the tambour against the artery. This tambour corresponds, as will be seen,

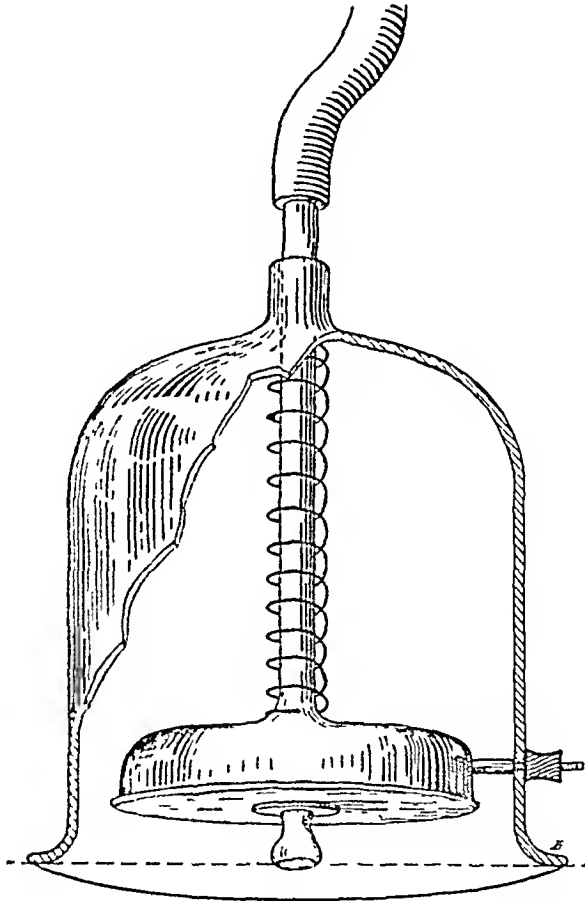


Fig 1—Carotid receiver. The tambour can be moved up and down, and fastened in a given position by means of a screw at the side.

rather closely to Marey's "explorateur a coquille ou a ressort," and to Brondgeest's pansphygmograph<sup>19</sup>. By this means, appropriate pressure against the soft part of the neck is obtained. The curves obtained with this equipment are read with a precision of from  $1/125$  to  $1/150$  of a second without the aid of any auxiliary apparatus. The interval

<sup>18</sup> By using this receiver no disturbing influence, from the waves in the jugular vein is seen.

<sup>19</sup> Brondgeest, P. Q. *Onderzoekingen gedaan in het Physiologisch Laboratorium der Utrechtsche Hoogeschool* 2 326, 1873.



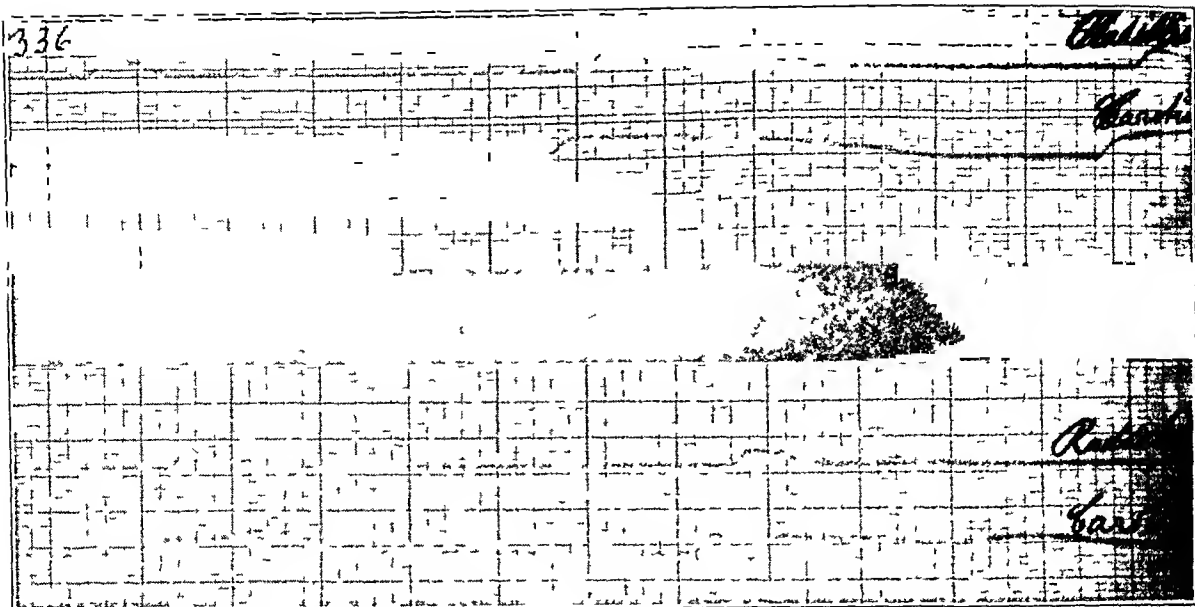


Fig 2 (Plate 336) —Curves of a normal person Above, the curve of the radial artery, below, of the carotid artery Speed of photographic plate, 38 meters a minute The duration between the ordmates equals 0.04 second The time interval between appearance of carotid and radial waves is of normal length ( $\frac{2}{25}$  of a second)

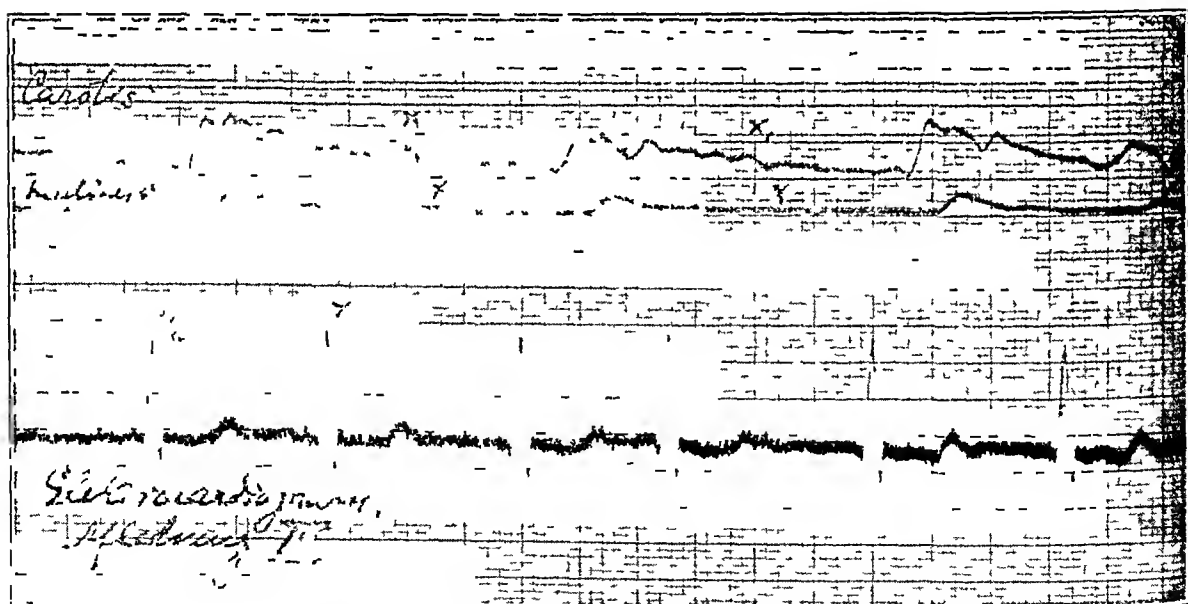


Fig 3 (Plate 380) —Curve of carotid and radial and electrocardiogram recorded simultaneously on a patient showing auricular fibrillation and perpetual arrhythmia Speed of photographic plate, 25 meters per minute Interval between carotid and radial waves normal Note that a certain number of heart beats are missing in the arterial system The contraction of the heart indicated by an X in the electrocardiogram gives only an indistinct wave in the carotid, and practically none in the radial In this way the pulse deficit (Robinson and Draper) is recorded graphically

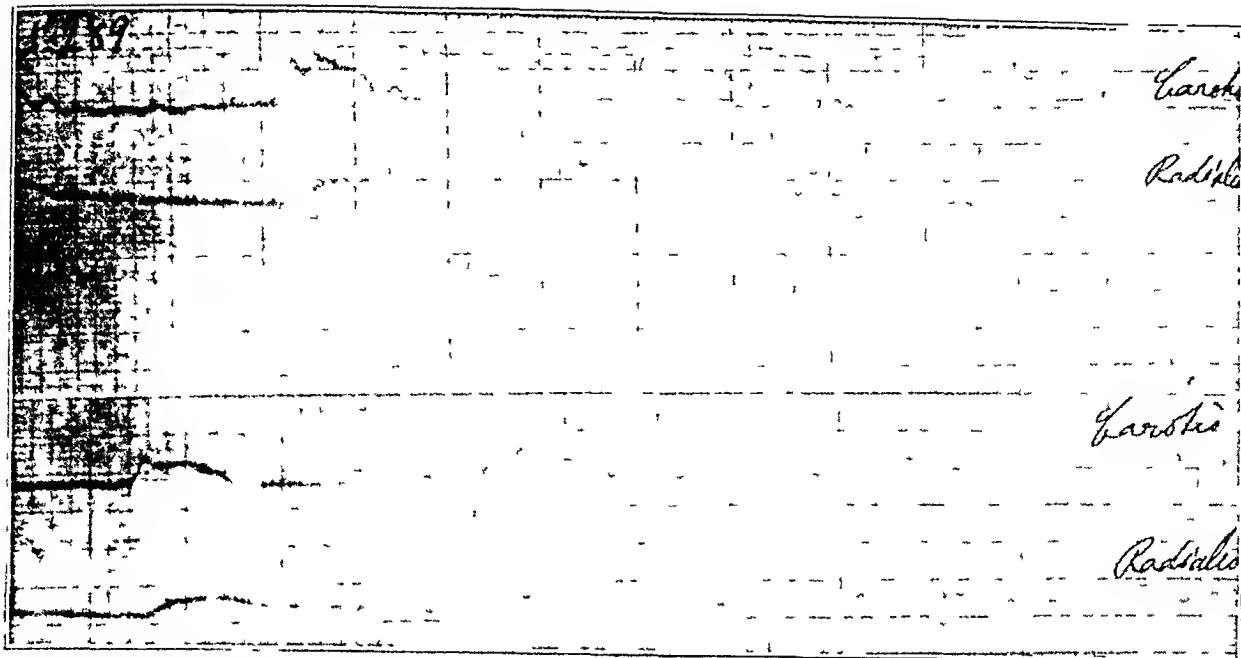


Fig 4 (Plate 289) —Curves from a patient suffering from chronic nephritis and arterial hypertension Speed of photographic plate, 39 meters per minute The time interval between the carotid and radial upstroke is  $\frac{1}{25}$  of a second, which is about one half of that normally found

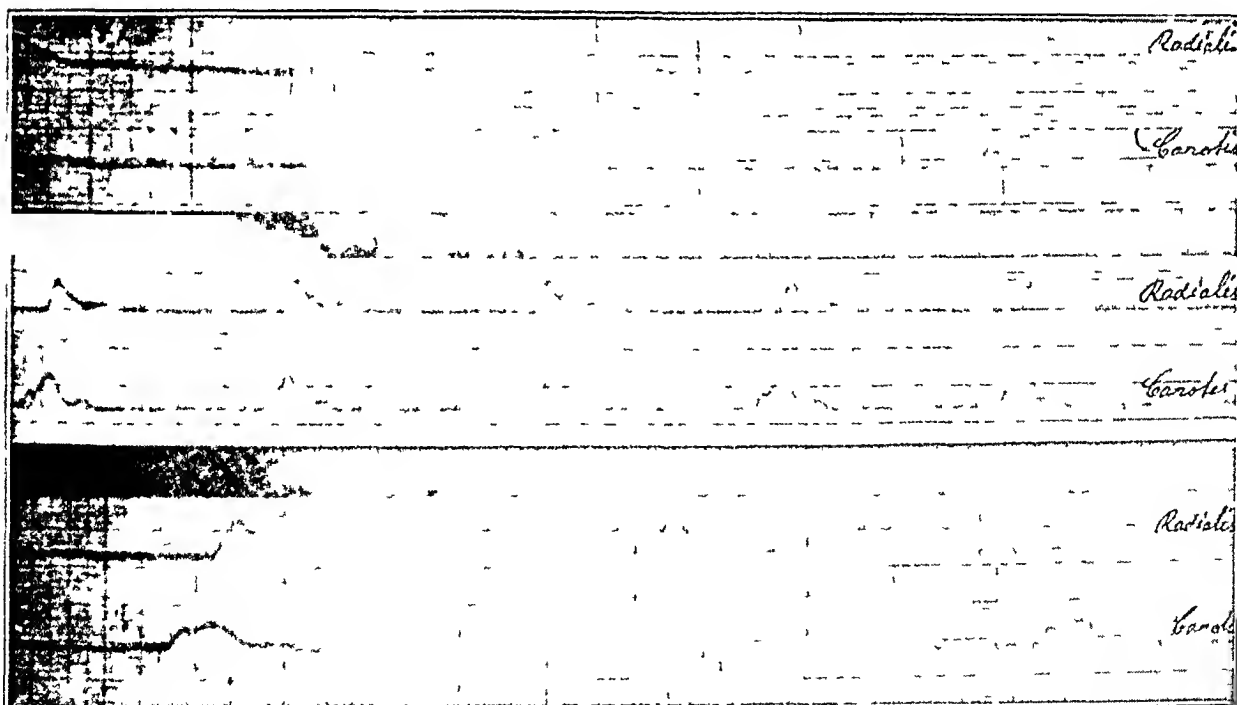


Fig 5 (Plate 413) —Three pairs of curves from a 28 year old patient suffering from aortic and mitral insufficiency The time interval between carotid and radial waves is normal The speed of plate, 42, 34 and 195 meters per second, respectively

separating the appearance of the two arterial waves being usually about  $2/25$  of a second in a normal individual, the error of the method will be about 10.5 per cent <sup>20</sup>

In Figures 2, 3, 4 and 5, are reproduced some examples of curves recorded by this method. The results of a rather large series of experiments on healthy persons as well as on patients, will be published later

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20 Hermann, L. *Handb d Physiol* 4 189, 1880

# THE RELATION BETWEEN INGESTED FAT AND THE LIPEMIA OF DIABETES MELLITUS\*

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Since patients with diabetes mellitus are more dependent on fat as a source of energy than are normal subjects, it is tempting to try to explain the hyperlipidemia that is so common in this disease on the basis of some theory that assumes a relationship between the amount of fat in the food and the percentage of lipoids in the blood. In the literature that has accumulated on this subject a tendency to assume this relationship is evident. In the Rockefeller monograph,<sup>1</sup> for example, the authors state that lipemia "is largely associated with the fat intake and with other diabetic symptoms." Ervin<sup>2</sup> states that "the lipemia of a diabetic will disappear with the elimination of fat from the diet." Bang<sup>3</sup> believed that the lipemia was, in part, alimentary. Joslin<sup>4</sup> suggests a relation between the high protein, fat diets of former days and the high degrees of lipemia reported, and states that "with restricted diet, particularly of fat, the blood fat rapidly falls." Bloor<sup>5</sup> has recently supported a suggestion of Allen's<sup>6</sup> that there is lacking a pancreatic hormone which is necessary for the proper removal of the fat from the blood. Bloor continues by conceiving that the factor of overwork must be taken into consideration in examining into the cause of diabetic lipemia, and that the patient has a fat tolerance which can be raised or lowered according as the ingested fat is restricted or increased. When large amounts of fat are ingested, the mechanism for the utilization of fat might be expected to break down, and he reported a case in which he alleges that a high lipemia resulted from a dietetic indiscretion which consisted chiefly in the ingestion of milk and cream.

In view of this belief, it was thought desirable to note the effect on the lipoidemia of diabetic patients of the high fat, low protein, low carbohydrate diets described by Newburgh and Marsh.<sup>7</sup> Since in these

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\* From Department of Internal Medicine, Medical School, University of Michigan.

1 Allen, F. M., Stillman, E., and Fitz, R. Total Dietary Regulation in the Treatment of Diabetes, Monograph of the Rockefeller Institute of Medical Research, No. 11, 1919, p. 143.

2 Ervin, D. M. Relation of Glycogen to the Pathologic Changes in Pancreatic Diabetes, *J. Lab. & Clin. Med.* **5** 146, 1919.

3 Bang, I. Diabetic Lipoidemia, *Biochem. Ztschr.* **94** 359, 1919.

4 Joslin, E. P. Diabetes Mellitus, *Oxford Med.* **4** 146, 1921.

5 Bloor, W. R. Lipemia, *J. Biol. Chem.* **49** 201, 1921.

6 Allen, F. M. Rôle of Fat in Diabetes Mellitus, *Am. J. Med. Sc.* **143** 313, 1917.

7 Newburgh, L. H., and Marsh, P. L. The Use of a High Fat Diet in the Treatment of Diabetes Mellitus, *Arch. Int. Med.* **26** 647 (Dec.) 1920.

diets the great majority of the calories are derived from fat, and since in each case the caloric requirement of the patient has been satisfied, the daily fat intake is relatively high, usually in the neighborhood of 4 gm per kilogram of body weight. This is more fat than is ordinarily consumed by the normal subject, and it seems certain that if there were a defect in the metabolism of fat similar to that in the metabolism of carbohydrate, a hyperlipoidemia must result. This should be particularly true in those subjects who demonstrated their tendency to hyperlipoidemia by presenting on admission to the hospital a gross increase over normal in their blood lipoids.

The patients selected for this study represented a number of different types of diabetes mellitus, varying in age, severity of the disease, duration of diabetic symptoms, previous treatment, degree of acidosis. The total lipoids of the blood were determined by the method of Bloor<sup>8</sup> which may be considered sufficiently accurate for comparative purposes and which would certainly demonstrate any large changes in lipoidemia.

#### REPORT OF CASES

CASE 1 (21-276) —An American farmer, 22 years of age, entered the hospital Feb 7, 1921, complaining of polyuria, weakness and loss of weight. A brother died of diabetes at 17. His past history is of no importance. His best weight was 164 pounds just before the onset of his diabetes, his weight at admission was 127 pounds. His symptoms appeared abruptly in August, 1920, and the diagnosis was made by his physician immediately. His diet was moderately restricted and he continued to lose weight and strength. Except for septic tonsils his physical examination was negative.

On a diet containing protein, 20 gm, fat, 85 gm, carbohydrate, 14 gm, and 900 calories, his urine became sugar-free on the fourth day, ferric chlorid reaction negative on the ninth day and his blood sugar normal on the sixteenth day. His diet was gradually increased until he was receiving daily protein, 43 gm, carbohydrate, 25 gm, fat, 230 gm, and 2,350 calories. This allowed him 39 gm fat per kilogram of body weight per day.

It will be noted from Chart 1 that his lipemia, which amounted to between 8 and 9 per cent, gradually fell and was still falling up to the time of discharge, in spite of the fact that he was eating large quantities of fat. The curve of his blood lipoids present three phases: A slow fall for about twenty-five days, a rapid fall during the next ten days and a slower fall during the remaining period. It is interesting to note that his food became sufficient to supply his caloric requirement at the beginning of the period when the fall in fat was most rapid, this was demonstrated by the cessation of loss of weight and the establishment of nitrogen balance.

CASE 2 (21-321) —An American farmer, 28 years of age, entered the hospital March 1, 1921, complaining of the usual diabetic symptoms. There was no family history of diabetes, except that a 4 year old son of his had had an occasional glycosuria. There was nothing of importance in his past history. Polyuria, polydipsia and polyphagia developed in August, 1914, when the patient was 21. During the following three months his weight fell from 160 to 113 pounds.

Treatment was not started until January, 1915. Four days of complete starvation followed by several days during which he was allowed green vegetables and two or three more days of starvation, a total of ten days, rendered

8 Bloor, W R. J Biol Chem 23 317, 1915

his urine sugar free. He was discharged on a diet which allowed him considerable freedom in the kinds of the foodstuffs that he ate but which was very much restricted in total calories. During the following two years he felt fairly well most of the time, although he had sugar in his urine frequently. Between the spring of 1916 and March, 1921, he was not free from sugar at any time, in spite of the fact that he was starved on five occasions for periods of from four to ten days.

During the month preceding his admission to our ward he suffered from epigastric distress, "heart burn" and nausea. His symptoms were sufficiently severe to make his home physician suspect peptic ulcer. His vision had failed

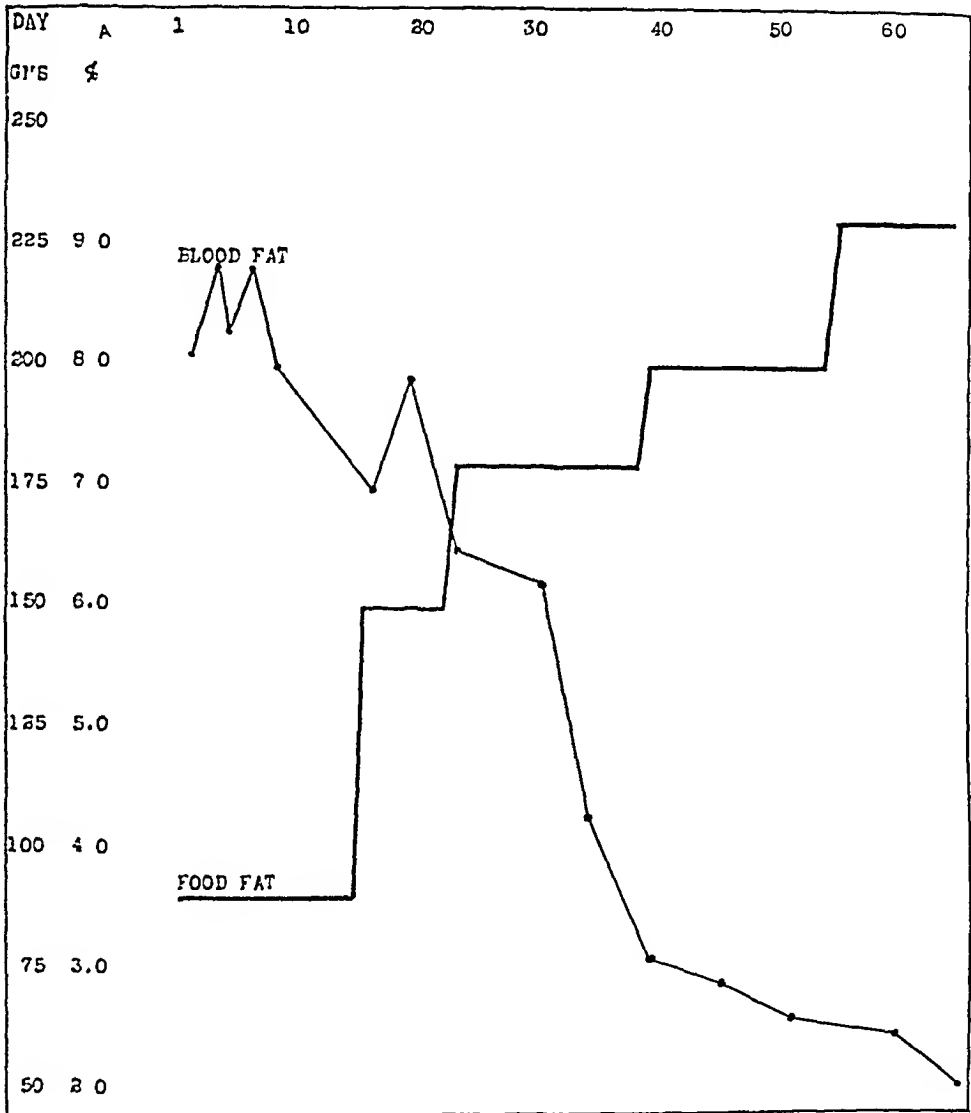


Chart 1—Graphic chart from Case 1

and he was badly constipated. On examination it was noted that he was decidedly stuporous and went to sleep while his blood was being taken for the laboratory examinations. Later he could not remember anything that had happened during the first day he was in the hospital. His breath had a decided acetone odor. His right knee jerk could be obtained only on reenforcement, and his left could not be obtained at all. His urine contained a trace of albumin, reduced Fehling's solution, and gave a heavy reaction with ferric chlorid. His blood sugar was 0.38 per cent and the carbon dioxide combining power of the blood plasma by the Van Slyke method was 37 volume per cent.

On a diet containing, protein, 20 gm , fat, 90 gm , carbohydrate, 14 gm , and 950 calories, there was a rapid relief of his acidosis, as shown by the rise in the carbon dioxide combining power of the blood plasma and the disappearance of the ferric chlorid reaction. There was no glucose in his urine on the eleventh day. His diet was increased until he was receiving, protein, 43 gm , fat, 220 gm , carbohydrate, 11 gm , and 2,200 calories. While the initial hyperlipoidemia in this case was not as marked as in Case 1, it was definite, and

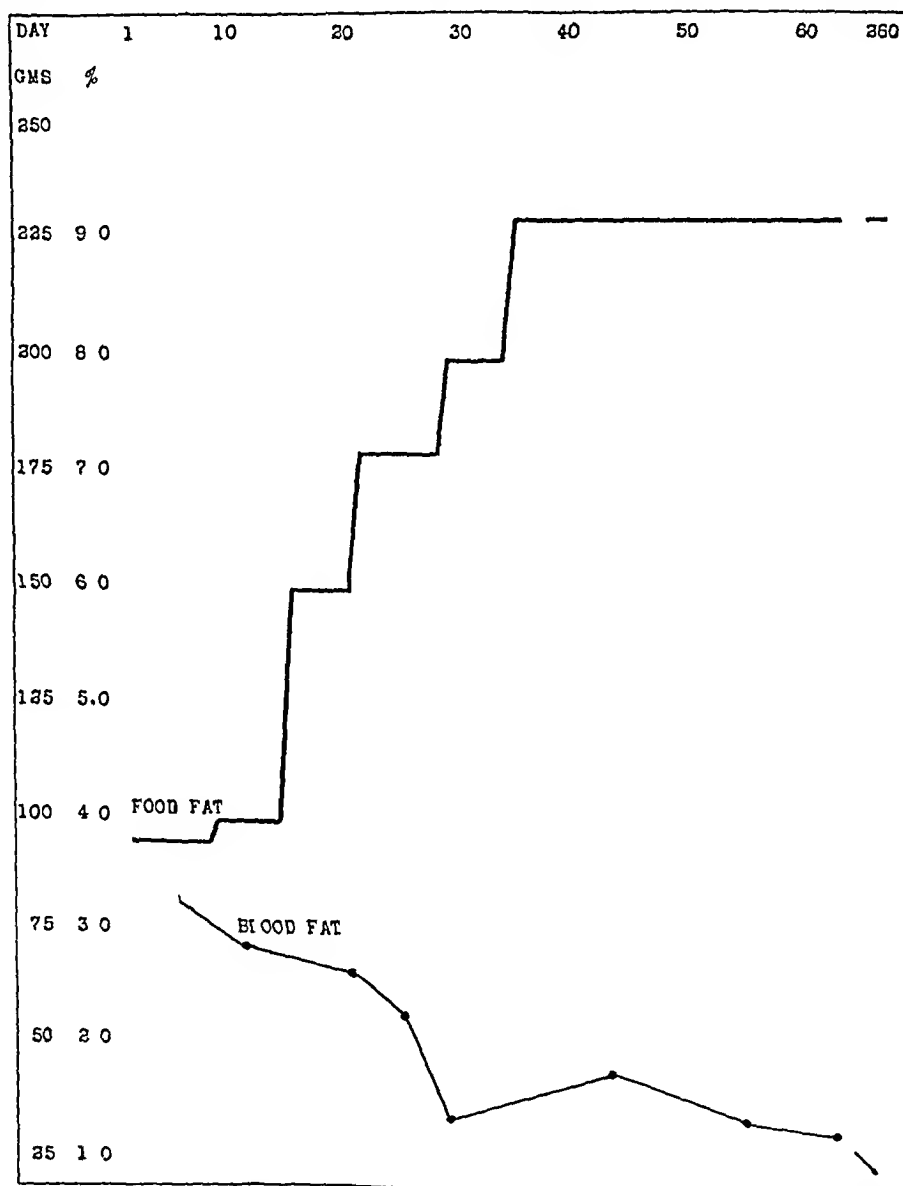


Chart 2—Graphic chart from Case 2

the determinations were made over a much longer period of time, there being nearly nine months between the first and last blood lipid record. The fall was from about 33 to 1 per cent.

CASE 3 (21-678)—An American clerk, 19 years of age, entered the hospital March 24, 1921, complaining of the usual diabetic symptoms. There was no history of diabetes in the family and nothing of importance in his past history. The disease had developed abruptly fifteen months before, and during the first three months he lost 30 pounds in weight. In spite of severe restriction in his diet, there was no improvement in his symptoms. Twelve days before

he came to us he was starved for seven days but did not know whether he became sugar-free. There had been some numbness of his feet and for two months he had had boils on his legs. On examination, evidence of advanced bilateral pulmonary tuberculosis was found and this complication was confirmed by roentgenograms and sputum examination.

There was no acidosis at any time, and the urine became sugar-free on the third day. The fall in blood lipoids as the food fat was increased is shown in Chart 3. The diet of the last period recorded on the chart contained, protein, 30 gm, fat, 180 gm, carbohydrate, 15 gm, and 1,800 calories, which allowed him 43 gm of fat per kilogram of body weight.

CASE 4 (21-1392)—An American merchant, 35 years of age, entered the hospital May 19, 1921, complaining of loss of weight, weakness, polyuria and

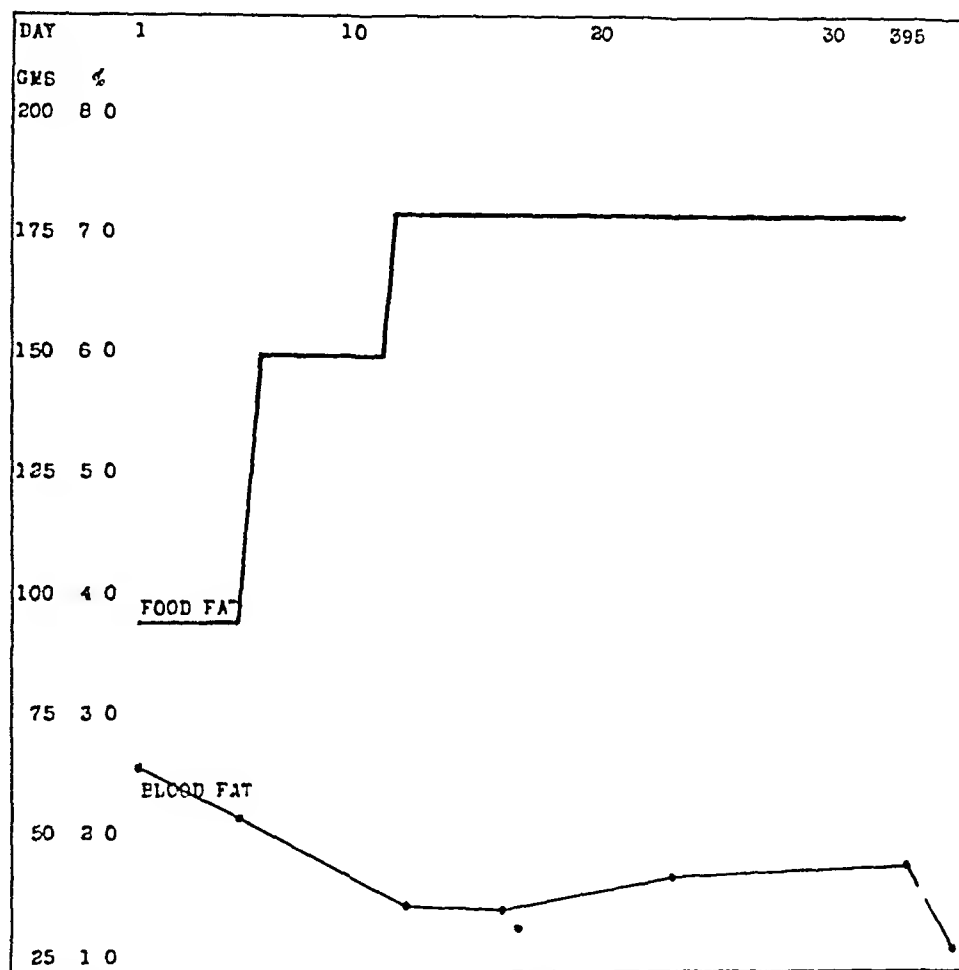


Chart 3—Graphic chart from Case 3

polydipsia. His symptoms developed abruptly in January, 1918, when he was 32 years of age. Glycosuria was found, and he became sugar-free on a rather liberal diet. After a few weeks he was advised to return to a normal diet, symptoms and glycosuria promptly reappeared. He again became sugar-free on the liberal diet and adhered to it about a year.

During the following year he increased his food intake and frequently found sugar in his urine. During this second year of his diabetes he had frequent night sweats, with one attack of pain in the lower left chest lasting some weeks. In February, 1920, he had influenza, and during the next few months his weakness progressively increased. In the fall of that year he spent four weeks in a sanitarium, and was discharged on a diet that was liberal, including a large quantity of gluten bread. From that time he grad-



ually went down hill, and since February, 1921, he had not been able to work. During the course of the diabetes his weight had fallen from 120 to 85 pounds. Physical and roentgen-ray examination demonstrated pathology in both pulmonary apices but no sputum could be obtained.

On a diet containing 20 gm protein, 90 gm fat, and 14 gm carbohydrate he became sugar-free on the eleventh day and the ferric chlorid reaction of his urine became negative on the fourteenth day. A moderate acidosis, demonstrated by the lowered carbon dioxid combining power of the blood plasma was promptly relieved. There was a gradually increasing edema during the first two weeks of treatment. His fat intake during the last period before discharge amounted to 38 gm per kilogram of body weight. The fall in total lipoids of the blood is shown in Chart 4.

CASE 5 (21-3458) —American, farm hand, 17 years of age, entered the hospital Nov 26, 1921, with a diabetes that had appeared abruptly in June of the same year with polyuria and weakness. In the interval his weight had fallen from 140 to 125 pounds. His family and past histories are of no importance.

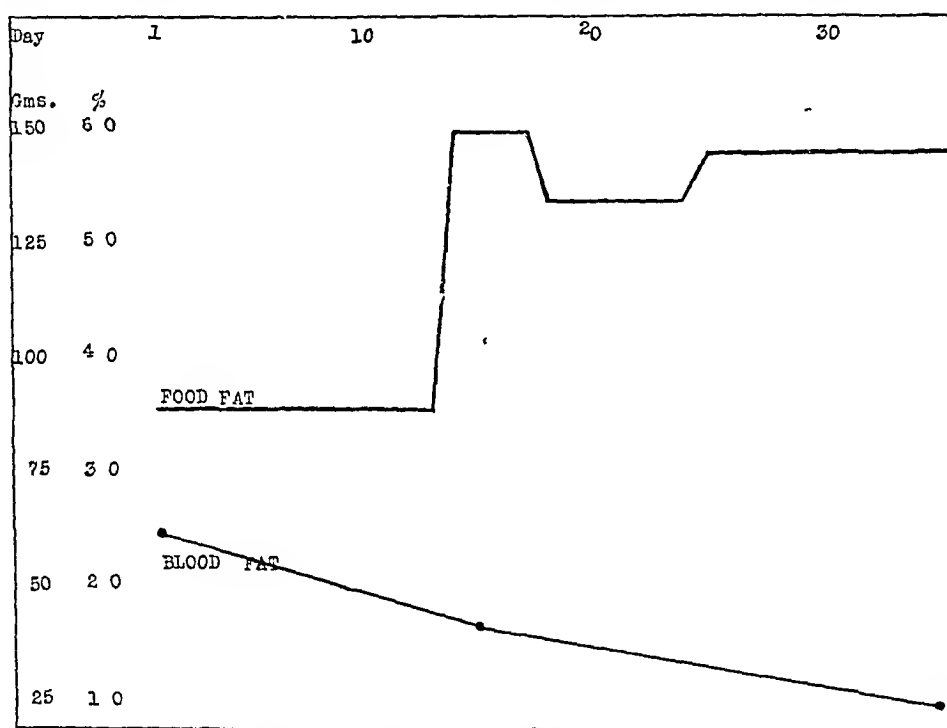


Chart 4—Graphic chart from Case 4

No significant abnormalities were noted in his physical examination. On a diet containing 19 gm protein, 88 gm fat, and 13 gm carbohydrate his urine became sugar-free on the eleventh day and the ferric chlorid reaction was negative on the seventh day. His diet was increased until he was receiving, protein, 55 gm, fat, 200 gm, carbohydrate, 30 gm, and 2,150 calories. At his weight of 121 pounds, this represented 36 gm fat per kilogram of body weight. His lipoidemia, which was not elevated at the beginning of treatment, remained at the same level throughout.

CASE 6 (21-2418) —An American housewife, 22 years of age, entered the hospital Aug 25, 1921, complaining of weakness and frequency of urination. Her family and past history was of no importance. Eight weeks before she went to her physician because of pain in the bladder and frequency of urination. Sugar was found in her urine. Weakness had been progressive and her weight fell from 120 to 93 pounds. Constipation had been obstinate. Nothing of importance was noted in the physical examination. The blood Wassermann and blood count were normal.

On a diet containing, protein, 18 gm, fat, 90 gm, carbohydrate, 13 gm, her urine was sugar-free on the fourth day, the ferric chlorid reaction was negative throughout. She was discharged from the hospital September 14 with a diet containing protein, 55 gm, fat, 220 gm, and carbohydrate, 25 gm. She remained sugar-free until the latter part of December when she returned to the hospital because of the reappearance of sugar in her urine.

On this occasion she became sugar-free in twenty-four hours, and her diet was rapidly increased to its former level. The blood lipid determinations were made during this period. It will be seen from Chart 6 that four months of a diet rich in fat did not increase her lipoidemia above the normal level. Two hundred and twenty grams of fat at a body weight of 100 pounds represents 4 gm of fat per kilogram of body weight.

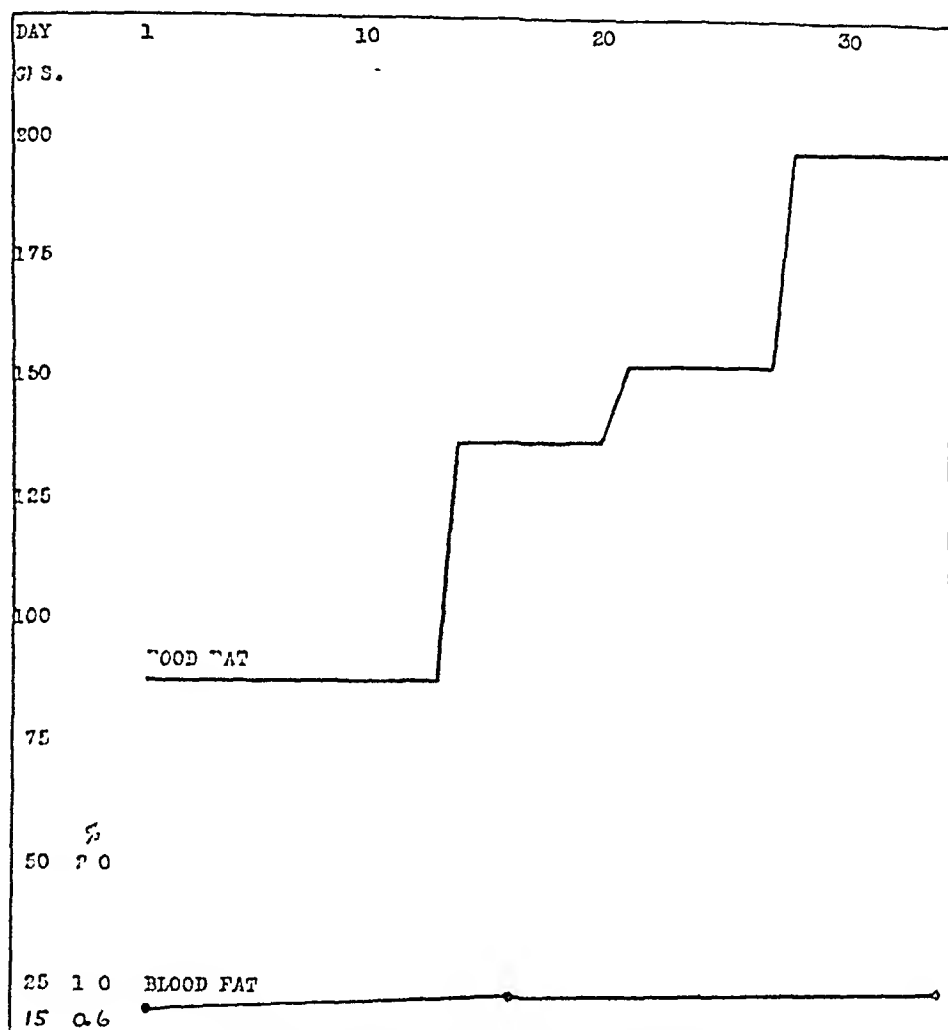


Chart 5—Graphic chart from Case 5

CASE 7 (22-2)—An American housewife, 47 years of age, entered the hospital Jan 2, 1922, with diabetes that had developed abruptly with cramps in the legs and polyuria in December, 1920. Glycosuria was found by the physician. Her weight had fallen from 168 to 121 pounds. Treatment had consisted of strict limitation of carbohydrate which did not keep her urine sugar free. Nothing of importance was noted on physical examination. On a diet containing 20 gm protein, 90 gm fat, and 13 gm carbohydrate, her urine became sugar-free on the third day and the ferric chlorid reaction was negative at the same time. Her diet was rapidly increased until she was receiving 55 gm protein, 210 gm fat and 34 gm carbohydrate. At her body weight of 119 pounds, this represented 4 gm fat per kilogram of body weight.

It will be noted from Chart 6 that her blood lipoids, which were slightly elevated at the initiation of treatment, fell promptly and remained only a little above normal

CASE 8 (21-3456) —An American housewife, 49 years of age, entered the hospital Nov 30, 1921 with diabetes complicated by ulcers on the legs Her family and past histories were without interest She had noticed her increased thirst and polyuria about eighteen months before, soon after her husband, whom she attended, died of carcinoma of the face Her symptoms had developed insidiously, and during the two years before admission her weight had fallen

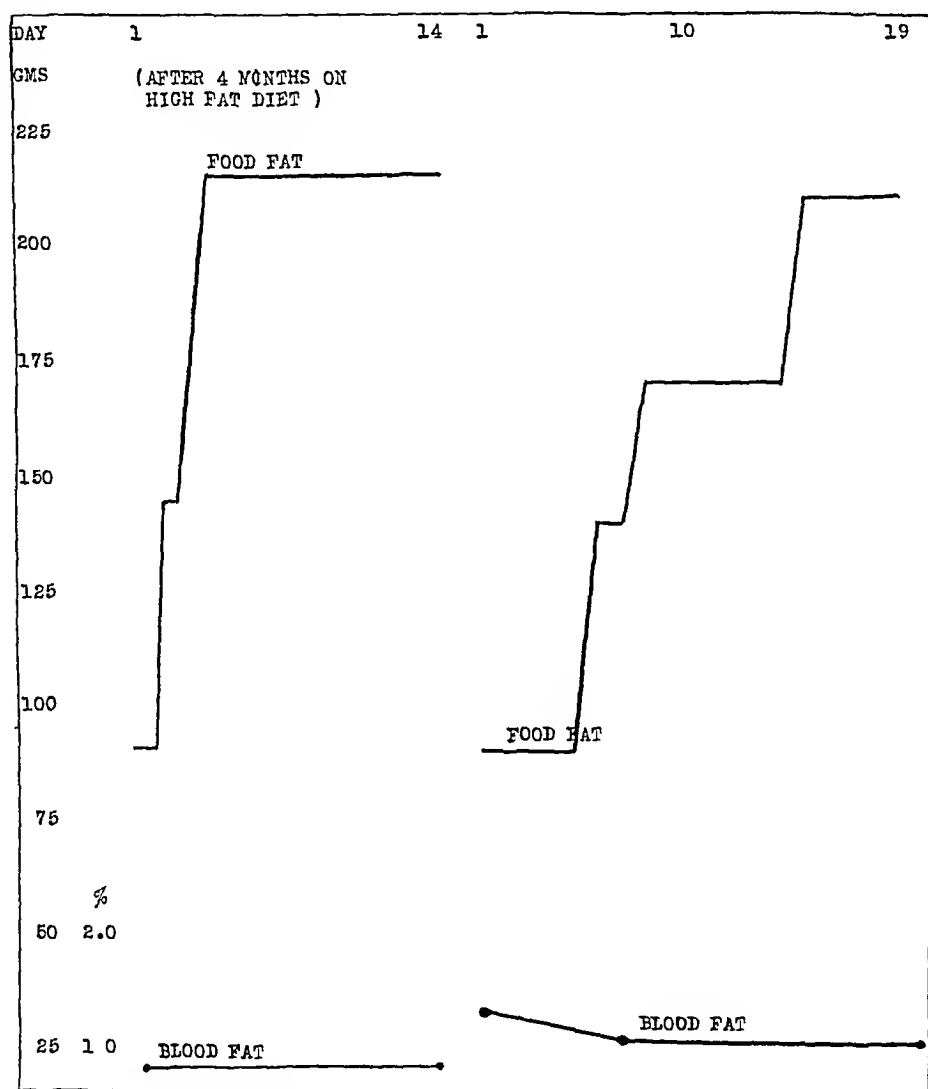


Chart 6—Graphic chart from Cases 6 and 7

from 165 to 101 pounds The ulcers on her legs had developed during the last two months There was a moderate degree of constipation, and her vision had been failing for two years On physical examination there was evidence of a moderate degree of arteriosclerosis and cardiac enlargement The knee jerks were markedly diminished and the Achilles reflexes could not be obtained On the anterior upper third of the left leg were three ulcers resembling very much in appearance gumous ulcers

On a diet containing 20 gm protein 85 gm fat and 13 gm carbohydrate her urine became sugar-free on the sixteenth day and the ferric chlorid reaction

was negative the next day. Her diet was increased until she was receiving protein, 55 gm, fat, 200 gm, and carbohydrate, 33 gm. At a body weight of 103 pounds this represented 4.2 gm fat per kilogram of body weight. It will be seen from Chart 7 that her blood lipoids were not elevated at any time.

CASE 9 (22-36) —An American farmer, 58 years of age, entered the hospital Jan 16, 1922, complaining of the usual diabetic symptoms. There was no familial history of diabetes, and his past history was unimportant. The symptoms had appeared abruptly two years before, and urine examination at this time revealed the presence of glucose. Treatment by the "Allen method"

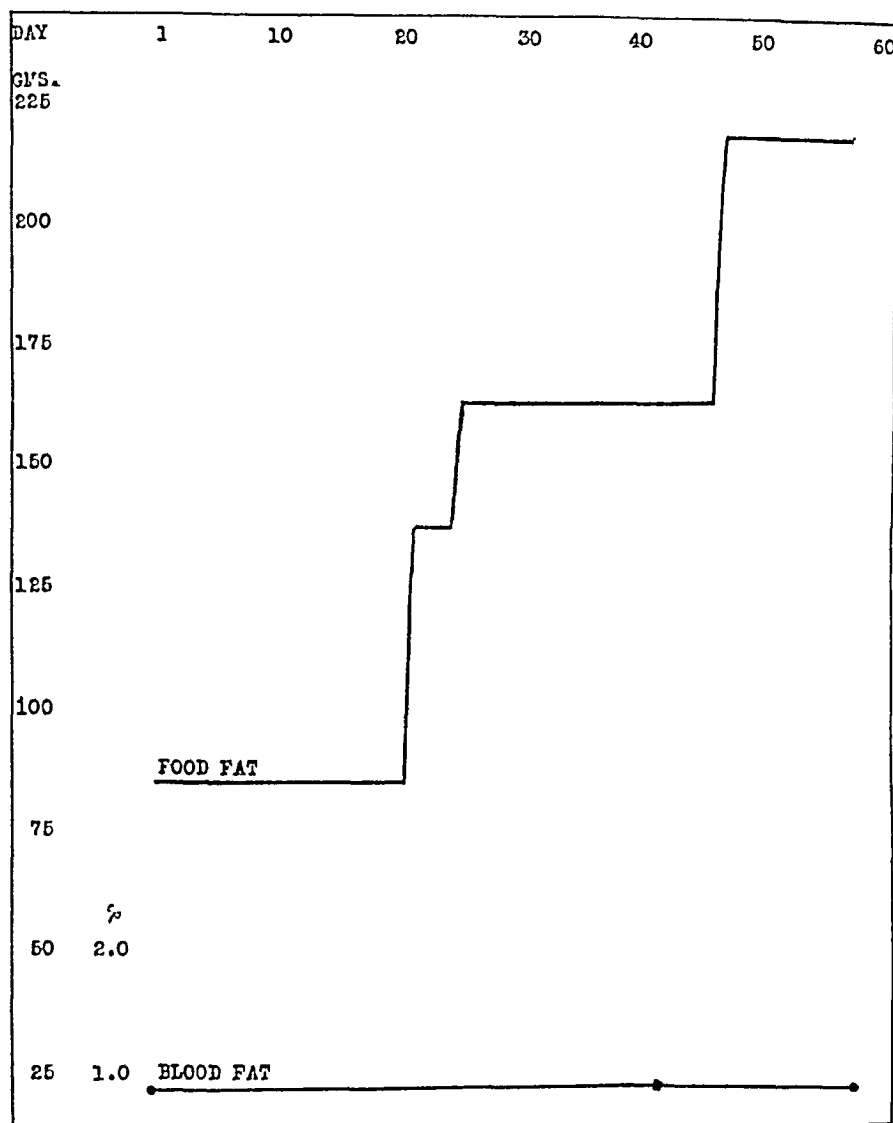


Chart 7—Graphic chart from Case 8

had been instituted on several occasions, but because of weakness the patient refused to adhere to the rigid regimen for more than thirty days at a time. In addition to the polyuria, polydipsia, and weakness, he complained of cramps in his legs, tingling of the feet, loss of weight from 140 to 102 pounds, failing vision, constipation, precordial pains and cardiac palpitation. Physical examination demonstrated slight cardiac enlargement and moderate arteriosclerosis, the knee-jerks were diminished and the Achilles reflexes could not be obtained. His urine, with a specific gravity of 1.046, contained a trace of albumin, glucose and a moderately strong ferric chlorid reaction. The blood sugar was 0.63. In the first twenty-four hour specimen there were 53.5 gm sugar.

On a diet containing protein, 18 gm , fat, 85 gm , carbohydrate, 13 gm , his urine became sugar-free on the fifth day Part of his record is shown in Chart 8 With a body weight of 110 pounds, his final diet allowed him 39 gm fat per kilogram of body weight per day Unfortunately, it was necessary for him to leave the hospital at the time indicated by the ending of the record It will be seen, however, that the percentage of blood lipoids, which was at an approximately normal level at admission, was not increased by the administration of a diet deriving most of its energy from fat

CASE 10 (22-610) —A 3 year old boy, American, entered the hospital March 6, 1922, with diabetes which had its onset in June, 1921, when the patient was 2 years of age His father's brother had diabetes The diagnosis was made

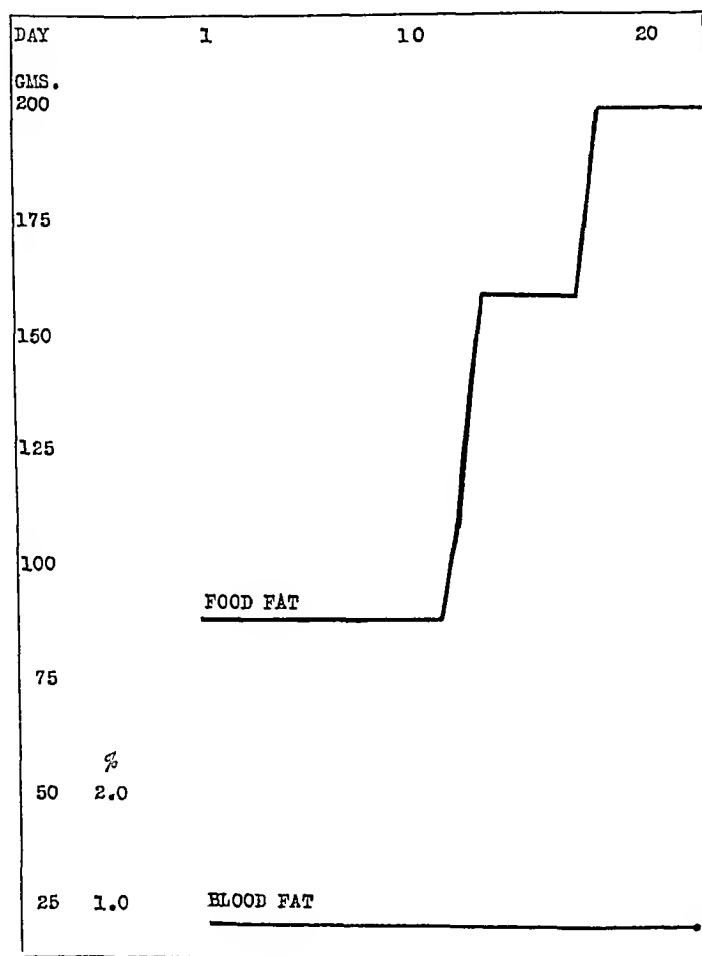


Chart 8—Graphic chart from Case 9

very soon after the onset of the symptoms, and rigorous dietetic treatment under the supervision of very competent physicians failed to control the glycosuria During most of the period between the onset and his admission to the University Hospital, his diet contained about 40 gm protein, 30 gm fat, and 25 gm carbohydrate, about 530 calories His urine was sugar free at times during the first few weeks but had not been at any time during the several months just previous to admission His weight had fallen from 32 to 29 pounds Examination was essentially negative On a diet containing protein, 8 gm , fat, 40 gm , and carbohydrate, 6 gm , he became sugar-free on the twelfth day His diet was increased to include 15 gm protein, 55 gm fat and 10 gm carbohydrate, without return of glycosuria This allowed him 4.2 gm fat per kilogram body weight His blood lipoids, which were slightly high at first, had fallen to a normal level by the thirty-third day (Chart 9)

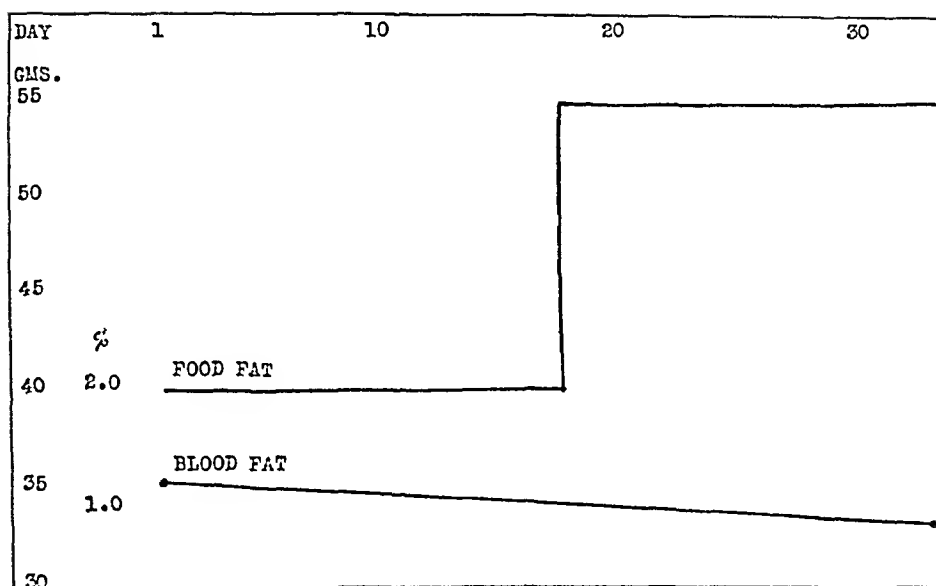


Chart 9—Graphic chart from Case 10

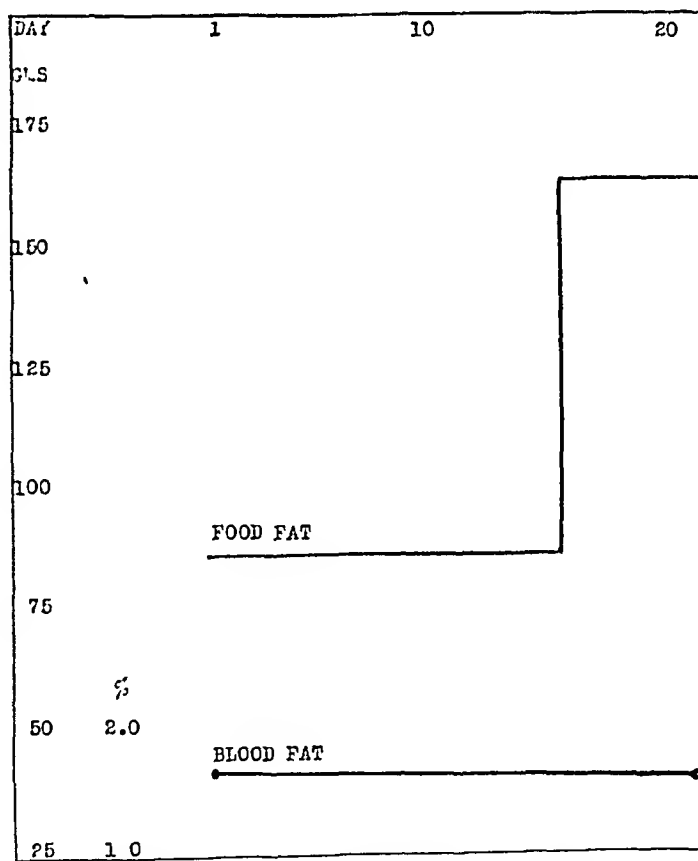


Chart 10—Graphic chart from Case 11

CASE 11 (20-1021) —An American farmer, 45 years of age, entered the hospital April 19, 1922, complaining of weakness and polyuria. His mother had died at 51 of diabetes mellitus. His past history was unimportant, except that after his mother's death he had frequent analyses made of his urine. In December, 1920, polyuria developed abruptly, and with this progressive weakness, with his weight falling from 155 to 135. His home physician stated that "even by withholding all carbohydrates" he had not been able to reduce the glucose content of the urine below from 3 to 6 per cent. For the past three years he had on excessive exertion had attacks of precordial pain which radiated to the left shoulder and were accompanied by shortness of breath. There was moderate cardiac enlargement and evidence of early arterial scler-

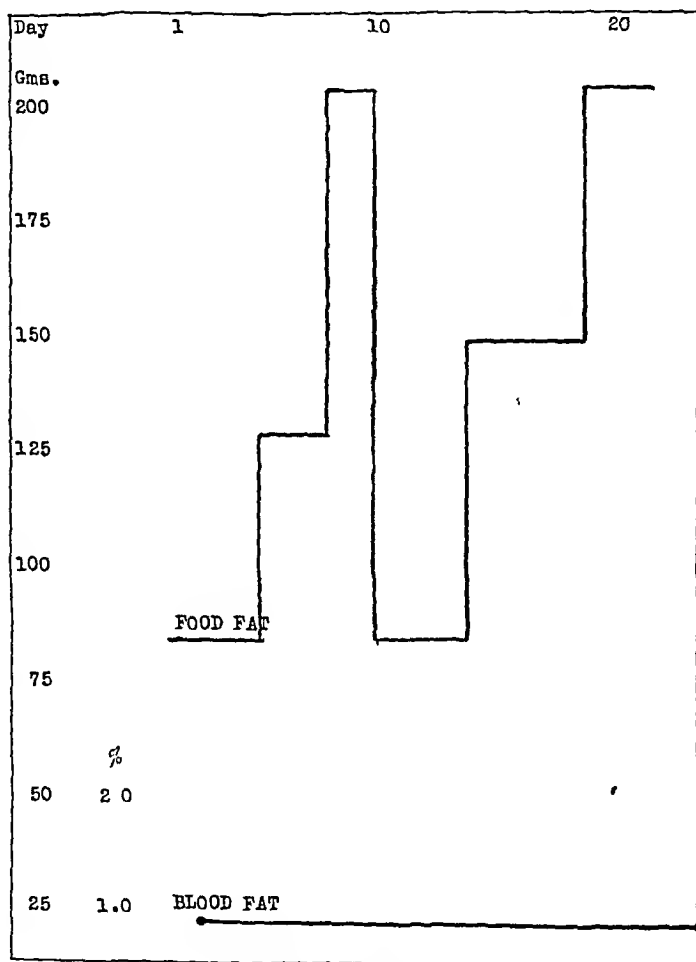


Chart 11—Graphic chart from Case 12

rosis. The urine contained sugar and gave a heavy reaction with ferric chlorid. The carbon dioxide combining power of the blood plasma (Van Slyke) was normal, and the blood sugar was 0.50 per cent.

On a diet containing 18 gm protein, 85 gm fat, and 15 gm carbohydrate his urine became sugar-free on the sixth day and the ferric chlorid reaction was negative a day later. Before our study of the case and the arrangement of his diet was completed he was called home by illness in the family, and further increases in his diet were made with the cooperation of his local physician. His blood lipoids, which were somewhat above normal at admission, did not fall during the brief period of observation, but neither did they rise (Chart 10).

CASE 12 (21-3573) —A retired merchant, 59 years of age entered the hospital, Dec 9, 1921, with a mild diabetes of two years' duration. Previous treatment had been negligible, and his weight had fallen from 175 to 145 pounds. There were no important complications. His glycosuria was irregular, and it was found that he was eating outside the hospital. After he was desugarized and his food allowance had been increased to about 200 calories a day, he broke diet, and he was started again at a lower level. The record of his ingested fat and blood lipoids is shown in Chart 1. The final diet allowed him was 31 gm of fat per kilogram of body weight per day. In spite of dietary irregularities, there was no increase in the blood lipoids.

From an examination of the records of these patients it is apparent that there was no increase in the lipid content of the blood during the periods of observation, and, of much greater significance, that in the patients in whom a hyperlipoidemia existed when they first came under observation, the total fat fell to approximately normal levels. This is in accord with the observations of Blatherwick<sup>9</sup> in three cases of mild diabetes. It is certainly very strong evidence that the prevalent assumption which postulates that diabetic hyperlipoidemia is dependant on the excessive ingestion of fat is unwarranted. The explanation of this phenomenon must be sought in some other unusual feature of the diabetic state.

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<sup>9</sup> Blatherwick, N. R. Observations on Blood Fat in Diabetes, *J Biol Chem* 49 193, 1921.



# DEFECTS IN THE MEMBRANOUS BONES, DIABETES INSIPIDUS, AND EXOPHTHALMUS, WITH REPORT OF A CASE

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The purpose of this paper is to report another case of defects in the membranous bones, diabetes insipidus, and exophthalmus, the seventh now in the literature, and to discuss some of the factors bearing on this disease

## REPORT OF CASE

*History*—A girl, aged 7 years, first came under observation June 27, 1919. Her parents were well, there were one older and two younger children, and no miscarriages. Patient was a full term baby, normal in the first year. In the second year she was weak and did not develop as did the other children, since when she has been underweight and underheight. At 6 years a tooth became infected, followed without pain by a discharge from the left ear, and an infection of the left mastoid, which was opened and drained in October, 1918. Following this, her mouth became very sore with a bullous eruption on the gums, necessitating the removal of some of the unerupted permanent teeth.

A month after leaving the hospital, i. e., seven weeks after the mastoid operation, she suddenly developed a marked thirst and polyuria, so that in a few days she was taking as much as four quarts of water during the night and was passing about one and one-half gallons of urine in twenty-four hours.

*Physical Examination*—Her weight was 30 pounds, height, 3 feet 8 inches. Skin very dry. Teeth and gums in bad condition, some of the permanent teeth have not appeared. A soft spot, oval in shape, measuring about 5x10 cm. can be felt in the right temporal bone. It has a well defined sharp, bony edge, it is not tender to slight pressure. Otherwise the skeleton seems normal. Exophthalmus of left eye. Heart, lungs, abdomen, and reflexes are all normal.

Urine. Very light color, specific gravity, 1.002, twenty-four hour amount about five liters, otherwise negative. Wassermann negative. Roentgenogram shows normal sella turcica.

*Clinical Course*—The patient was lost sight of until Oct. 13, 1921, her tenth year. It was noticed that her mouth improved after cutting down sugar and starch intake as she had been advised to do, and that the soreness of the gums returned as soon as sugar was taken. She felt well and acted like other children, except for the thirst and polyuria, and was considered bright in school, where she was, however, only in the second grade.

Her weight was now 36 pounds, height 3 feet 8½ inches. The left ear was still discharging slightly. No obesity, genitalia normal for her age.

Eye examination showed a definite left exophthalmus, no increase in the intraocular pressure, fields of vision normal, color sense normal.

The blood showed white cells, 8,000, stained spreads normal, and blood sugar 0.10 per cent.

*Urinary Findings*—A glucose tolerance test gave the result shown in Table 1. Only 15 gm. glucose were given instead of the usual amount, and even this made her gums very sore. It will be noted that the blood sugar was not abnormally increased by this amount. The amount of urine was not increased nor did sugar appear in it.

Urine collected according to the method of Mosenthal gave the results shown in Table 2, a reaction typical of diabetes insipidus. There is simply a large increase in the water excretion, with a consequent lowering of the

specific gravity Although the night urine is enormously increased, its relation to the day urine is normal Chlorids and nitrogen are excreted at a low concentration, but the total output is within normal limits

On another occasion urine was again collected in the same way but 25 gm sodium chlorid were given at 10 a m The result in Table 3 shows that chlorids are promptly and readily excreted, and that it is not necessary for this patient to increase the quantity of urine to get rid of this amount of chlorids

TABLE 1—GLUCOSE TOLERANCE TEST

Time	Blood Sugar, per Cent	Urine		
		Amount, Cc	Specific Gravity	Sugar
8 50	0 114	500	1 001	0
9 00 (15 gm glucose)				
9 30	0 150	25	1 001	0
10 30	0 180	400	1 001	0

TABLE 2—RESULTS FROM EXAMINATION OF URINE COLLECTED ACCORDING TO MOSLINTHAL'S METHOD

Time	Amount, Cc	Specific Gravity	Chlorids		Total Nitrogen	
			Per Cent	Gm	Per Cent	Gm
8-10 a m	165	1 005				
10-12 m	220	1 006				
12- 2 p m	375	1 002				
2- 4 p m	370	1 008				
4- 6 p m	370	1 004				
6- 8 p m	720	1 004				
Total day	2,170		0 09	1 95	0 18	3 91
Total night	1 105		0 05	0 55	0 16	1 77
Total 24 hours	3,275			2 50		5 68

All specimens negative for albumin and sugar

TABLE 3—CHLORID EXCRETION

Time	Urine		Chlorid	
	Amount, Cc	Specific Gravity	Per Cent	Gm
10 a m	325	1 001	0 13	0 42
Sodium chlorid 25 gm				
12 m	700	1 001	0 14	0 98
2 p m	600	1 007	0 47	2 82
4 p m	575	1 002	0 08	0 48
7 p m	650	1 000	0 07	0 46
10 p m	800	1 002	0 14	1 16
Total day	3 710			6 30
Total night	1,800	1 004	0 14	2 52
Total 24 hours	5,510			8 82

*Roentgen-Ray Examination*—Roentgen-ray examination of the entire skeleton showed striking changes in the membranous bones Large areas of the bones of the skull are rarified or completely absorbed leaving areas with well defined, scalloped edges where there is apparently no bone at all These areas vary in size The largest is about 10x5 cm in the right temporal bone They are scattered all over the skull including the bones of the orbit It is of some significance to note that the bones forming the bridge of the nose are not involved, nor is the sella turcica, which is normal A similar area is present in the lateral border of the left ilium where there is a semicircular defect about

6 cm in diameter extending from the anterior superior spine to the acetabulum. Here, as in the cranial defects, there is complete absence of lime salts. There is deformity of the lower jaw with abnormal position of the teeth and apical infection of some teeth. The long bones, the vertebrae the carpal and tarsal bones, etc., are nowhere involved.

The changes noted are quite different from the changes found in syphilis, tuberculosis, osteitis fibrosa, Paget's disease, bone cysts, or sarcoma. In the complete absence of lime salts these lesions suggest

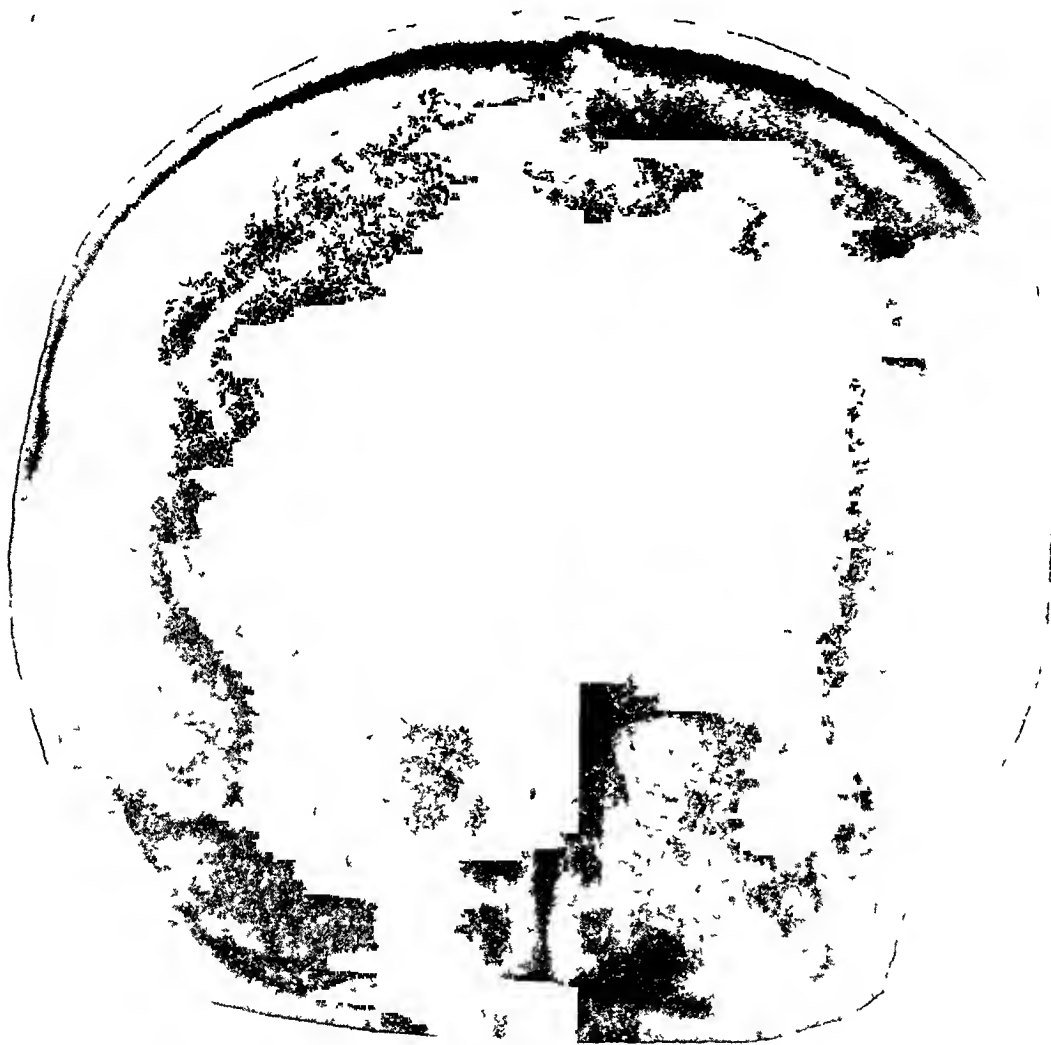


Fig 1—Front view of skull, showing extensive bony defects

the changes found in some cases of bone metastases of carcinoma, and with this exception no difficulty should arise in making a differential diagnosis.

*Effect of Pituitary Extract*—Oct 19, 1921, pituitary extract, hypodermically, was administered, at first 1 cc once a day, later 0.5 cc twice a day, and was continued, with only an occasional intermission, for the next three months. At first the usual striking response was obtained. The urine decreased to 1,600 cc. October 21, 1,400 cc. October 22, 1,900 cc. October 29. On days when no pituitary extract was given the output increased to 3,300 cc.,

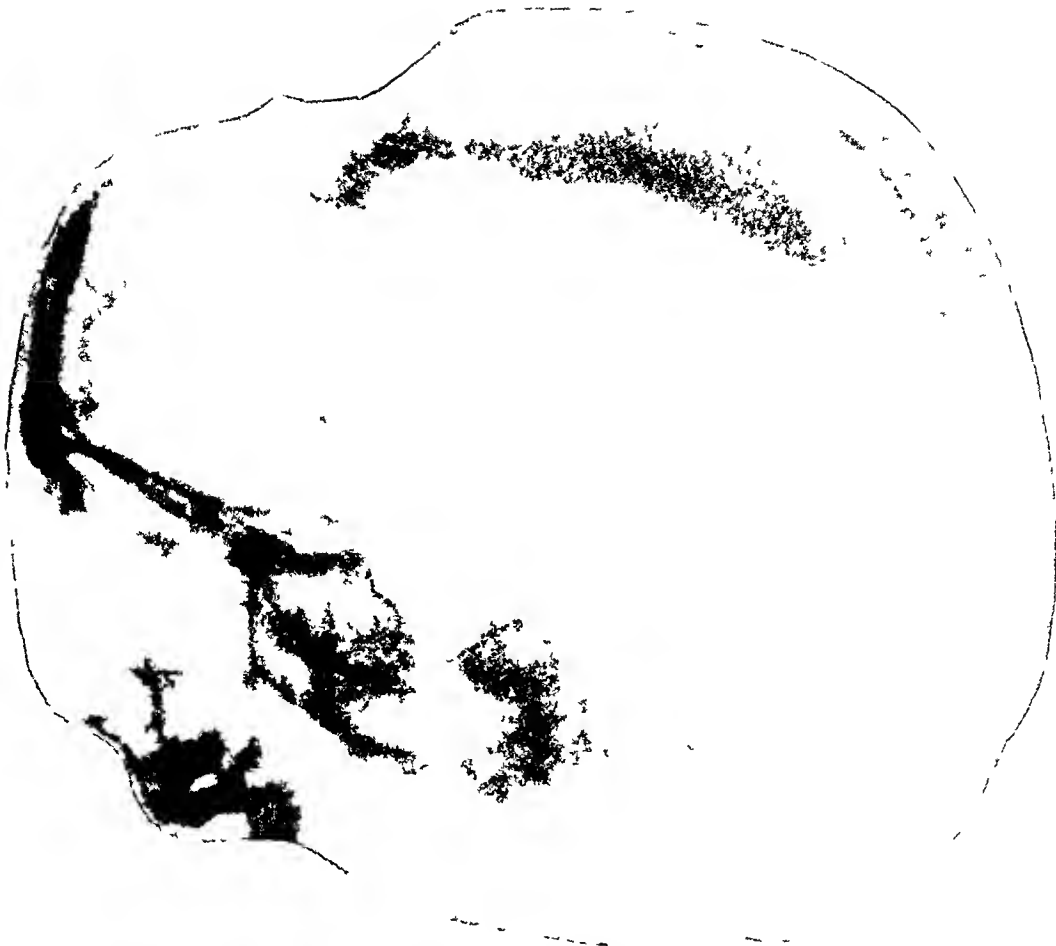


Fig 2—Side view of skull, showing extensive defects with normal sella turcica



Fig 3—Pelvis with large defect in left innominate bone

3,400 cc, 4,300 cc, etc November 11, however, even with 0.5 cc pituitary extract twice in the day, the patient excreted 5,700 cc urine, and from then to Jan 6, 1922, the output never went down very strikingly. The amounts measured ranged from 2,000 to 5,000 cc in addition to which specimens were lost every night. It is true that on days when no pituitary extract was given the amount went to 6,000 cc, but it seemed obvious that the patient was not responding to pituitary extract in a satisfactory manner. January 6, she developed great weakness, substernal pain, dyspnea and nausea, symptoms apparently due to the pituitary extract, and since then no injections have been given.

March 11, 1922, she had been passing from 3,000 to 6,000 cc urine per day. She was now 10 years old. Her weight was 39 pounds, the average for a girl of 5 years, her height was 3 feet 9 inches, the average for a girl of 7 years. There was no apparent change in the bony defects of the skull.

Here, then, was a girl showing dwarfism, diabetes insipidus, defects in the membranous bones, and unilateral exophthalmus.

#### DISCUSSION

It is not our purpose again to review the literature on this subject, which has been done admirably by Christian<sup>1</sup> and also by Hand<sup>2</sup>. A

TABLE 4—REPORTED CASES

Case Reported by	Sex	Age	Bone Defects	Polyuria	Sella	Exophthalmos
Hand <sup>2</sup>	M	3	+	+	No X ray	+
Hand (Key) <sup>2</sup>	M	7	+	+	No X ray	+
Hand (Luburg) <sup>2</sup>	M	4	+	+	Normal	+
Christian <sup>1</sup>	M	5	+	+	Defect	+
Schuller <sup>3</sup>	M	16	+	0	Normal	+
Schuller <sup>3</sup>	F	4½	+	+	Defect	+
Author	F	10	+	+	Normal	+

careful search failed to reveal any new cases. For reference the six cases already reported and the one here reported are outlined in Table 4.

Slight similarity is found in a series of ten cases reported by Barber,<sup>4</sup> under the title "Renal Dwarfism." These are cases characterized by the development from the tenth to the seventeenth year of typical rachitis with chronic interstitial nephritis and, in eight of the ten cases, marked increase of thirst, all of the patients exhibiting some degree of dwarfism. The bone defects did not, however, involve the membranous bones, exophthalmus was not present in any of the cases, nor was the polyuria as striking as in this series, and they are therefore omitted.

1 Christian, H. A. Defects in Membranous Bones, Exophthalmus, and Diabetes Insipidus. Contribution to Medical and Biological Research. Paul B. Hoeber, New York 1 390, 1919.

2 Hand, A. Defects of Membranous Bones, Exophthalmus and Polyuria in Childhood, *Am J M Sc* 162 509, 1921.

3 Schuller, A. Ueber eigentartige Schadeldefekte in Jugendalter, *Fortschr a d Geb d Roentgenstrahlen*, 23 12, 1915.

4 Barber, H. Renal Dwarfism, *Quart J M* 14 55, 1921.

In the seven cases here tabulated the constancy of defects of the membranous bones, of polyuria and of exophthalmus is so evident that one seems justified in grouping them together. No new theories are advanced here to account for the condition, but it seems pertinent to call attention to certain observations that have already been made. One is tempted at first to attribute the condition somehow to disease of the hypophysis, because the hypophysis is thought to exercise control over the growth of the skeleton and because it is so firmly regarded as the seat of the trouble in diabetes insipidus. Indeed, the exploitation of the hypophysis advanced to such a state that it became necessary recently for Cushing<sup>5</sup> to file new credentials for it in no uncertain terms. About the only evidence that diabetes insipidus originates in the hypophysis is that pituitary extract temporarily relieves the polyuria and that polyuria occasionally follows hypophyseal operations. Evidence like the first, so often advanced, is, of course, entirely unreliable. The fact that a drug relieves a symptom is no sign that the symptom is due to a deficiency of the drug. One wonders why the suprarenals have not been more often blamed for asthma because epinephrin relieves the paroxysms. Moreover, the polyuria following hypophyseal operations is too inconstant to be of much value. We have very little evidence that pituitary extract is discharged into the circulation at all. It seems probable that it is a product of glia cells of nothing more than pharmacologic interest.

The work of Bailey and Bremer<sup>6</sup> is of especial importance in this connection. They have shown that whereas polyuria following experimental lesions of the hypophysis is usually temporary, lesions of the hypothalamus may produce a permanent polyuria and polydipsia, sometimes even associated with adiposogenital dystrophy. These conditions can be produced after the temporary polyuria following hypophyseal operations has subsided. This polyuria from lesions of the hypothalamus has apparently all of the characteristics of diabetes insipidus in man. It seems probable that tumors of the hypophysis produce diabetes insipidus in man only when they press upward on the brain stem, thereby involving centers in the hypothalamus, the tuber cinereum, or the floor of the fourth ventricle.

In considering diabetes insipidus it is important to keep three factors in mind. First, is the factor in the central nervous system already referred to, second, the functional capacity of the kidney must

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5 Cushing, H. Disorders of the Pituitary Gland, *J. A. M. A.* **76** 1721 (June 18) 1921.

6 Bremer, F., and Bailey, P. Experimental Diabetes Insipidus and Genital Atrophy, *Endocrinology* **5** 761, 1921. Experimental Diabetes Insipidus, *Arch. Int. Med.* **28** 773 (Dec.) 1921.

be considered, and third the maintenance of the water balance of the body. There is little evidence to show that the kidney function is impaired, much to show that it is not impaired. Nitrogen products and chlorids in the blood are maintained at a normal level as long as the patient may take all the water that he desires. When sodium chlorid is administered, it is excreted quickly, sometimes at such a high concentration that increased diuresis does not occur. If water is withheld, the rise in blood chlorids is very great, sometimes even reaching 1.03 per cent,<sup>7</sup> but at times the power of salt concentration is retained as high as three fold.<sup>8</sup>

Veil<sup>9</sup> investigated most thoroughly the chlorid factor in these cases. He concludes that there are two forms of diabetes insipidus, the one showing hyperchloremia after the ingestion of sodium chlorid, the other hypochloremia. He shows that puncture of the midbrain produces polyuria of the first type, i. e., hyperchloremia with hypochloruria, while puncture of the fourth ventricle produces polyuria of the second type, i. e., hypochloremia with hyperchloruria. This again complicates the rôle of the hypophysis in diabetes insipidus.

The water balance of the body is regulated both by the satisfaction of thirst and by the excretion of water by the kidneys. These are to some extent independent functions. Polyuria may occur without any increase in water intake as it does when patients with diabetes insipidus for any reason go into coma, while excessive thirst may occur without any great loss of fluid from the body. It is the function of the kidney in all animals that have kidneys to keep the osmotic pressure of the blood at the primordial pressure of sea water. If water is ingested by a healthy person, diuresis quickly occurs, if salt is taken, thirst is promptly felt. The cause of the sensation of thirst is still unknown. Cannon's attractive theory of irritation of the nerve endings in the throat seems entirely refuted by the work of Wier, Larson, and Rowntree<sup>10</sup> who showed that anesthetizing the throat has no effect on thirst. If more water is taken than can be excreted promptly, it is probably stored in the cells of the tissues. For Cohnheim showed that animals could be given physiologic solution of sodium chlorid to the extent of 90 per cent of their body weight without the development of edema. Incidentally, it was found later that it is necessary to inject the fluid intermittently at about the rhythm of the heart. If injected in a

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7 Socin, C. Ueber Diabetes Insipidus, *Ztschr f klin Med* **78** 294, 1913

8 Goldberg and Herz. *Rev de med* **33** 310, 1913

9 Veil, W. H. Intermediare Vorgänge bei Diabetes Insipidus, *Biochem Ztschr* **91** 317, 1918

10 Wier, Larson, and Rowntree. Studies in Diabetes Insipidus, Water Balance, and Water Intoxication, *Arch Int Med* **29** 306 (March) 1922

continuous stream, edema does occur, and if the secretion of urine is in any way impaired, toxic symptoms occur, among them headache, vomiting, dyspnea, cramps, twitching, ataxia and convulsions. In diabetes insipidus, even with the large intake and the large output, the water balance is ordinarily well maintained. As in normal persons, we have very little evidence of a nervous control of the kidneys.

Returning to the case reported, the relation of the polyuria to the bone defects is puzzling. Embryologically, the pituitary bears a relation to the membranous bones of the skull. In the lower vertebrates, such as the amphioxus, the vertebral column is composed of the notochord. In the human the notochord, which has become the intervertebral discs, ends at the sella turcica. From here the axial portion of the skeleton is continued forward to form the base of the occipital bone and the body of the sphenoid, both of which are formed from cartilaginous bone. The other bones of the cranium are, however, formed in the mesenchyme of the head, where ossification takes place directly into tissue like the connective tissue of the skin. Embryologically, then, the sella turcica and the membranous bones of the skull lie just anterior to the end of the axial skeleton.

The rôle of infection in the etiology of diabetes insipidus deserves more consideration than it receives in the literature. In this case it will be noted that the onset of the polyuria occurred a few weeks after an operation on an infected mastoid. In one other case of the series there was an infected ear and in the case reports of two other patients sore mouths and bad teeth are mentioned. Two other cases of polyuria are known, neither yet reported in the literature, both of which were associated with mastoid disease. In one case the polyuria persisted for a week after operation, until a subdural abscess evacuated itself through the mastoid incision. The other case also followed an operation on an infected mastoid. What part the infection played and what part pressure on and injury to the base of the brain played is, of course, impossible to say, but it will be of interest to know what the incidence of infection in the mastoid, the ear, and the mouth is in polyurias of the diabetes insipidus type.

#### CONCLUSIONS

1. A case is reported exhibiting some degree of dwarfism, diabetes insipidus, defects in the membranous bones of the skull and pelvis, and exophthalmus.

2. Pituitary extract hypodermically controlled the polyuria temporarily. After a time the effect of pituitary extract diminished. It had no effect on the bone defects.

3. The etiology of this disease is unknown.



4 Diabetes insipidus is not a disease entity, but more likely a clinical syndrome of disease of the base of the brain caused by pressure, injury, or infection

We wish to thank Mr H W Dachtler, of Toledo, for his careful roentgenologic studies of this patient

# ORTHOPNEA <sup>1</sup>

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AND

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Numerous theories have been advanced from time to time to account for orthopnea, but there has been surprisingly little discussion of the subject. Hewlett <sup>1</sup> sums it up as follows

It is well known that patients suffering from dyspnea, and particularly those suffering from cardiac dyspnea, cannot breathe as comfortably when lying down as when sitting up. The dyspnea which necessitates an upright posture is spoken of as orthopnea. The exact cause of orthopnea is not definitely understood. According to the views of earlier authors, the sitting posture allows better fixation of the shoulders, and this favors the use of the accessory muscles of inspiration, but Hofbauer showed that these patients experienced their chief difficulty in expiration rather than inspiration. The upright posture is a more favorable one for expiration, because the anterior abdominal wall is pushed out by the lower position of the abdominal viscera, and when it contracts during forced expiration it works at a better mechanical advantage. In the sitting posture, also, the diaphragm takes a lower position. As a result of this, the thoracic cavity is enlarged and the size of the lungs is increased. It seems probable that this pulmonary distention assists the pulmonary circulation by increasing the caliber of the pulmonary capillaries. Finally, a high position of the diaphragm may lessen the aperture traversed by the inferior vena cava, and it may thus obstruct the return flow of blood from the lower parts of the body. A lower position of the diaphragm, such as occurs in the sitting position, would remove this obstruction. It is difficult, at the present time, to say which of these possible advantages is the most important in contributing to the relief which dyspneic cardiac patients frequently experience in the sitting posture.

The thought occurred to one of us (C D C) that orthopnea might be dependent on an excessive reduction in the vital capacity of certain patients when they lie down. On searching through the literature to learn the normal percentage of reduction, few observations were found on this particular phase of the subject of vital capacity, and the standards of comparison did not seem satisfactory. Furthermore, several observations which we made at random on persons about the laboratory, tended to refute the flat statement that the vital capacity is always smaller in the lying posture. Consequently, it was decided to check the subject on a large series of normal subjects. The results have been recorded in a previous communication <sup>2</sup>

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\* From the Department of Medicine, Western Reserve University, Lakeside Hospital

1 Hewlett. *Monographic Medicine* 1:375

2 Christie and Beams. *Arch Int Med* 30:34 (July) 1922

We found from this series of observations on 290 normal men and women, between the ages of 20 and 30, that there is 55 per cent less vital capacity in the lying than in the sitting posture for all groups when averaged, that approximately 80 per cent of all normal persons have a smaller vital capacity lying than sitting, and that with rather obese normal women this difference may amount to as much as 20 per cent. We further found that nearly 20 per cent of the normals of our series have a vital capacity which is practically the same when they recline as when they sit. Some persons can even expire more lying down than sitting, and in two instances of big healthy and intelligent medical students we found that they had nearly 10 per cent more vital capacity lying down than sitting. We did not observe any differences in type of chest which seemed to account for these disparities. We concluded further from these observations that normal persons of the same sex and same body surface have surprisingly near the same vital capacity, in fact, those with variations constitute only about 10 per cent. It was shown also that as the body surface increases, there is a fairly constant increase in the vital capacity, that is to say, a normal female between 20 and 30 years of age, with a body surface of from 1.4 to 1.5 square meter, has a vital capacity of 2,700 c c, and with each increase of 0.1 square meter the vital capacity goes up 125 c c. With normal males between 20 and 30 years of age, with a body surface of from 1.6 to 1.7 square meter, there is an increase of 350 c c in the vital capacity for each additional 0.1 square meter added to the body surface. When these results were all totaled, it was found that normal females between the ages of 20 and 30 years have a vital capacity of 1,970 c c for each square meter of body surface, and healthy males of the same ages have a vital capacity of 2,470 c c for each square meter of body surface. These results agree closely with those published by West<sup>3</sup>. Given, then, a patient with a reduction in vital capacity, these latter figures allow us to estimate fairly accurately the normal vital capacity that persons should have. It is only necessary to know the body surface, and if the patient be a female multiply the estimated body surface by 2,000 c c, and if a male multiply the estimated body surface by 2,500 c c.

It is our belief that there will not be genuine orthopnea without a great reduction of the vital capacity, the most common cause of which is cardiac disease, although it may be reduced greatly as the result of other conditions, such as pulmonary tuberculosis (and, of course, the more advanced the greater the reduction), pleurisy with effusion, large lung or mediastinal tumors, bronchiolar spasm, and finally paresis of the external muscles of respiration, such as is seen in syringomyelia.

and anterior poliomyelitis. It is possible, therefore, to have genuine orthopnea in any of the above mentioned conditions providing they encroach sufficiently on a healthy lung to cause a very severe reduction in the vital capacity.

A simple example will serve to bring out the point which we have in mind. Given a patient with severe cardiac disease, whose vital capacity when he sits erect has been reduced to 1,000 c c—if he has a body surface of 1.6 square meter, his normal—a vital capacity should be 4,000 c c (body surface  $\times$  2,500 c c). He has, therefore, only 25 per cent of his vital capacity left, or a 75 per cent reduction. This reduction is quite sufficient to use up any luxury which he had, and he is, therefore, down to the irreducible minimum in the sitting posture. What happens if this same patient lies down? There is an immediate reduction in his vital capacity by 55 per cent of 4,000, that is, 220 c c, which would be the normal difference between his sitting and lying postures. But when he already has a reduction of the vital capacity to 1,000 c c, this 55 per cent reduction or 220 c c becomes a 22 per cent reduction, and he has in the supine position a remaining vital capacity of only 780 c c, which is wholly inadequate for his needs. The whole luxury was used up in the first great reduction, and now if he lies down and incurs this additional encroachment it is immediately felt.

Orthopnea is commonly seen in severe cardiac disease, so commonly, in fact, that the condition has almost come to be looked on as something peculiar to and coincident with severe heart lesions. It is quite obvious, of course, that such is not the case, for there is a great variety of clinical conditions which will give the proper stage settings, as it were, for typical orthopnea, quite as genuine and characteristic as is ever encountered in severe cardiac disease. The idea that orthopnea must be associated with severe cardiac lesions has been responsible, we believe, for the suppression of facts which shed considerable light on this symptom.

That several important factors are to be taken into consideration as probable causative agents in the production of orthopnea is apparent. It is our conviction, however, that reduction in vital capacity is the primary factor. Without a severe reduction the condition cannot exist, and the more extreme the reduction the more likely the condition is to appear. Contributory or associated conditions which increase the severity of orthopnea are moisture in the lungs and painful inflammation of the pleura, both of which stimulate the cough reflex and thereby cause increased work on the part of the organism, with consequent increase in metabolism and the necessity for increased ventilation on the part of lungs already sorely embarrassed from the great reduction in the vital capacity. It becomes apparent, then, that any other factors causing

an increase in the metabolic rate and, therefore, demanding increased pulmonary ventilation would be contributory causes, as fever, restlessness, or exercise

With these fundamental considerations, we believe it is quite apparent that orthopnea may be present in any condition which gives rise to severe reduction in the vital capacity of the lungs, with the likelihood of its being still greater if any of the contributory causes are present. It is not strange or peculiar, then, that it should be so often and so commonly seen in cardiac diseases, for in this condition we constantly find a reduction of the vital capacity, and the more severe the embarrassment of the heart, the greater the reduction of the vital capacity. This has long been known, but the admirable work of Peabody during recent years has emphasized the fact and greatly amplified our knowledge of the subject.

We believe that orthopnea may be subdivided into (1) orthopnea of choice, and (2) orthopnea of necessity. In reality, the two conditions are precisely the same, the only difference being one of degree. "Orthopnea of choice" is by far the more common. In this condition the patients prefer to sit up, but it is not essential to their well being for they can lie down and remain comfortable. In fact, we have made observations on these patients with regard to their breathing, and find that they are practically just as well off lying down as sitting. There is no apparent increase in their respiratory rate or volume and no increase in the pulse rate. From closely questioning many of them we have come to the belief that much of the "orthopnea of choice" is simply a matter of the patient's being just a bit easier in the upright position. That is to say, when he lies down and the additional 5.5 per cent of his normal vital capacity is taken away, he notices it and becomes apprehensive. This is particularly true if he becomes restless in bed and thereby increases his metabolism, which, in turn, causes a demand for increased respiration from a vital capacity that is much reduced.

"Orthopnea of necessity" is, as the name implies, a condition which the patient brings about for self-preservation. These cases are in the minority but they are not uncommon. The patients assume the upright posture to take advantage of every available cubic centimeter of vital capacity. We believe them to be persons who normally have a considerably smaller vital capacity in the lying than in the sitting posture, but with many of them one does not have to assume a bigger reduction than the average of 5.5 per cent to explain their discomfort. Take as an example, a person like the one discussed previously, whose normal vital capacity of 4,000 c c has been reduced by disease to 1,000 c c. If he should lie down there would be a further reduction to 780 c c, which

would, of course, be wholly inadequate. Add to that a fever or an exhausting cough, both of which would increase the metabolic rate or the demand for greater pulmonary ventilation, and it is easy to see that this patient could not survive for a very long time. If the patient for any reason lies down in bed, there is an immediate struggle on his part to get up. His respiratory rate goes up, if it is possible, there is acceleration of the pulse rate, cyanosis increases, and the patient becomes greatly alarmed, struggles frantically for air, and looks with intense horror on what appears to him as impending disaster. This is the picture in our minds of "orthopnea of necessity."

It is obvious, then, that orthopnea is largely a question of vital capacity. If there is for any reason just about sufficient reduction to use up the *luxus*, the additional loss of 55 per cent of the original normal vital capacity on assuming the lying position is immediately felt by the patient, and he prefers sitting up to preserve even so small an amount, for then he is not quite so much aware of his respiratory needs. But in another case, if the *luxus* is entirely used up when the patient is in the sitting posture so that respiration is already increased, and he is now for any purpose put in a supine position, the additional loss of 55 per cent of vital capacity becomes unbearable, and unless it is immediately restored disaster will follow.

It is not uncommon to see two patients with cardiac lesions equally severe only one of whom has orthopnea. From all external evidences, the patients should be afflicted equally, but such is not the case. This has mystified us many times, but we think the explanation is simple. They may have their vital capacity reduced to the same degree, but the one who has orthopnea falls among the 80 per cent who suffer a varying degree of reduction on lying down, while the other comes in the smaller group of those who have practically the same or even a greater vital capacity when lying down. We have repeatedly had confirmation of this fact. For instance, one orthopneic patient with his vital capacity reduced to 1,200 c c has, when he lies down, a vital capacity of, say, 950 c c. This patient is one of the great 80 per cent group of those who get a reduction of their vital capacity when they lie down. Another patient with just as severe a cardiac lesion has no particular orthopnea though his vital capacity also is reduced to 1,200 c c. When this patient lies down it will be found that his vital capacity is still 1,200 c c or may be even 1,400 c c, so that there is obviously no need for him to sit, as he is quite as comfortable lying down as sitting.

There are all degrees of this condition, but it seems obvious to us that "orthopnea of choice" and "orthopnea of necessity" are two clearly defined symptoms and their recognition is a simple procedure. We further believe that the establishment of the fact that perhaps 20 per

cent of people breathe as much, if not more, when lying down is the final answer to the mystifying question of why some patients with severe cardiac disease do not have orthopnea

#### DISCUSSION

When this work was first under consideration, we were sceptical of our ability to get the maximum expiratory effort when a patient with intense orthopnea was reclining. We have, in fact, had failures owing to our inability to gain the cooperation of the patient, but we have four chief reasons for thinking that the results herein recorded are as nearly accurate as can be obtained under the conditions (1) Repeated attempts were made, and in each instance the maximum that the patient breathed sitting or lying was the value chosen (2) Our forty-two patients with reduced vital capacity from disease lost only 5.9 per cent of their estimated vital capacity when lying down, while our 290 normal subjects lost 5.5 per cent of their vital capacity when lying down (3) Approximately 80 per cent of our 290 normal had under the same conditions within 50 c.c. of their sitting vital capacity or even more, while of our patients with vital capacity reduced from disease, 81.5 per cent expired less lying down and 18.5 per cent came within 50 c.c. or breathed more lying down than sitting (4) There is only one patient in the series (J. W., Table 1) who lost more than 10 per cent of his estimated normal vital capacity on lying down. He was our worst case of "orthopnea of necessity," but we had among our normal males those who lost as much as 10 per cent on lying down, and in the case of the females, two of them who were obese showed a loss of 20 per cent of their vital capacity in the supine position. So it may be that J. W. in health would have reacted as did these normal subjects. However, in the face of evidence to the contrary, it is quite likely that the acute distress of most of the patients in this group did vitiate our results to a certain extent, for if we take only the group of cases with "orthopnea of necessity," we find that they lose on lying down 8 per cent of their estimated normal vital capacity, which may indicate that they lost a little more as a result of their disease. However, to establish the validity of our claims, we do not need such a great percentage of loss due to posture as 26.5 per cent, or one-fourth of the remaining vital capacity, which is the average reduction for all patients in this group.

We must add that all of the patients with "orthopnea of necessity" tabulated in Table 1 had some of the contributing causes of orthopnea, such as fever, cough, pain, nervousness, all of which would increase metabolism and thereby create a greater demand for pulmonary ventilation from a greatly inadequate ventilating surface.

It should be noted also that all of these patients in Table 1 breathed less lying down than sitting, and we believe most of them when in health would have responded like the 80 per cent of normals

All of the figures in Table 1 were totaled in our averages, except those in the last two observations on M T, which were made after he had improved

The cases of "orthopnea of choice," as tabulated in Table 2, were very similar to those in Table 1, the difference being largely one of degree. They could lie down and remain fairly comfortable, but they preferred to sit upright. Many of these patients had doubtless had "orthopnea of necessity," but were better when we saw them as the result of rest or therapy. All of them lost an additional amount of their vital capacity on lying down, with the exception of one (T S). She said she was more short of breath lying down, but it is to be doubted, because she showed no increase in pulse rate or respiratory rate after lying down twenty minutes. She was very nervous and apprehensive and died subsequently.

Doubtless some of these patients cited in Table 2 would have had "orthopnea of necessity" had there been any contributory cause, such as increase in metabolism. But clinically they were not so acutely distressed as were those in Table 1. One patient (N) nicely illustrates this point. While she had a gross reduction of her vital capacity from pleural effusion (massive) and cardiorenal and vascular disease, yet she was free from any of the exciting causes of an increase in metabolism. She sat up in bed day after day without an ache or pain, and breathed in apparent comfort.

Table 3 shows a group of patients with varying degrees of reduction in their vital capacities but with no orthopnea. It will be noted that (except three patients who will be discussed later) none of them showed the extensive reductions from disease that were tabulated in the two other tables, nor did they show a great percentile loss of vital capacity due to lying down. In fact, with the exception of one case this group contained all of the 18.5 per cent who showed no change or a gain in vital capacity on lying down.

The second patient in Table 3 (A J) was a man with extreme loss of vital capacity due to very marked cardiac decompensation, as severe, in fact, as in many of the cases with "orthopnea of necessity." This patient, it will be noted, was not orthopneic, and could and did lie down perfectly well. It was proved that his vital capacity was decidedly greater lying than sitting. This man, we believe, belongs to the 20 per cent group of our normal individuals who breathe as much or more when lying.

The results from the two observations made on Mrs. T were not included in our totals, since we believe the upright vital capacity was



TABLE 1—ANALYSIS OF CASES OF ORTHOPNEA OF NECESSITY

Name	Age	Sex	B S	Estimated		Estimated Reduction Due to Posture 55 % of Sitting Vital Capacity	Actual		Per Cent of Reduction from Normal	Difference Due to Posture	Per Cent of Reduction Due to Posture	Condition of Patient
				Vital Capacity Females, B S $\times$ 2,000 Males, B S $\times$ 2,500			Vital Capacity as Result of the Disease					
				Sitting	Lying		Sitting	Lying				
M J	45	F	16	3,200	3,024	176	1,085	883	66	202	18.6	Decompensation, rales at bases, liver engorged, blood pressure 230/110, edema
L P	30	F	17	3,400	3,213	187	1,062	667	69	395	38	Edema, rales, tender liver, cough, double aortic, fever, endocarditis
T S	35	M	183	4,575	4,323	251	1,149	883	76	266	23	Evident decompensation, liver engorged, rales at bases
M T	55	M	16	3,690	3,487	202	1,213	883	58	330	28	Edema, branch block
			16	3,690	3,487	202	1,276	1,128	58	148	11	Prefers to sit up
			16	3,690	3,487	202	1,450	1,340	51	100	7.8	After therapy, can lie down, edema less
			2	5,000	4,725	275	1,107	567	78	540	48	Extreme decompensation, aortic insufficiency and stenosis
I W	26	M	2	3,200	3,024	176	1,107	905	66	202	18	Auricular fibrillation, decompensated chronic myocarditis
L S	43	F	16	4,388	4,146	242	1,318	1,107	70	211	16	Cyanosis, edema, liver engorged, rales
S S	56	M	195	4,750	4,488	261	1,800	1,400	62	400	22	Rales, cough, fever, aortic insufficiency and stenosis
M W	35	M	19	2,700	2,551	148	1,062	667	61	395	38	Myocarditis, bronchitis, fever
T C	55	F	15									

These two determinations are not figured in the totals

TABLE 2—ANALYSIS OF CASES OF ORTHOPNEA OF CHOICE

Name	Age	Sex	B S	Estimated		Estimated Reduction Due to Posture 55 % Of Sitting Vital Capacity	Actual		Per Cent of Reduction from Normal	Difference Due to Posture	Per Cent of Reduction Due to Posture	Condition of Patient
				Vital Capacity			Vital Capacity					
				Females, B S $\times$ 2,000	Males, B S $\times$ 2,500		Sitting	Lying				
S W	43	F	17	3,400	3,213	187	1,758	1,537	49	221	12.6	Cardiovascular and renal, some edema, few rales at bases
N	35	F	15	3,000	2,835	165	774	709	78	64	8.2	Pleural effusion, both chests, no moisture, no cough, cardiovascular and renal
E S	64	F	15	3,000	2,835	165	971	774	68	197	20	After withdrawing some fluid
M O	72	F	168	2,700	2,551	148	1,362	1,107	50	255	18	Liver tender, slight edema
J P	60	M	17	3,024	2,907	116	1,340	1,122	59	218	15.4	Some decompensation
A G	50	M	177	3,825	3,615	210	1,500	1,402	61	98	6.5	Luetic myocarditis, cerebral sclerosis, few signs
T S	44	F	18	3,983	3,764	219	1,550	1,250	60	300	19	Chronic myocarditis, edema, fluid, right pleural cavity
G S	48	M	205	3,600	3,402	198	1,626	1,626	55	0	0	Slight edema, etc
G M	64	M	203	4,613	4,359	254	2,100	1,900	55	200	9.5	Endocarditis, auricular fibrillation, slight decompensation
F S	50	F	163	4,307	4,071	251	2,829	2,633	48	196	7	Edema, tender liver, rales at bases, etc
S S	45	M	18	3,260	3,021	179	1,475	1,150	55	325	22	Fluid, right pleural cavity, edema
F S	45	M	19	4,488	4,252	261	2,306	2,010	52	286	12	No sign of decompensation
J B	61	M	165	4,500	4,252	204	2,130	1,974	53	156	7.3	Slight edema, gallop rhythm
F P	37	M	17	3,713	3,409	233	1,491	1,213	60	281	12	Moderate decompensation, metabolic rate 11 per cent above normal
				4,250	4,016		3,115	2,829	27	286	9.1	Mitral disease no increase in respiratory rate no signs of failure

TABLE 3—ANALYSIS OF CASES WITH REDUCTION IN VITAL CAPACITY WITHOUT ORTHOPNEA

Name	Age	Sex	B S	Estimated Vital Capacity Males, B S $\times$ 2,500		Estimated Reduction Due to Posture 5 1/2 % of Sitting Vital Capacity	Actual Vital Capacity as Result of the Disease		Per Cent of Reduction from Normal	Difference Due to Posture	Per Cent of Reduction Due to Posture	Condition of Patient
				Sitting	Lying		Sitting	Lying				
W K	70	M	1 95	1,388	1,116	212	2,845	2,523	35	322	11	Chronic bronchitis, emphysema, left ventricle, hypertrophy
A J	49	M	1 8	4,050	3,827	223	1,171	1,318	72	+137	+11 6	Chronic myocarditis, decompensated, emphysema
M B	11	M	1 08	2,700	2,551	148	1,868	1,626	31	242	13	Congenital heart, cyanosis, no decompensation
M M	30	M	1 85	1 625	1,371	254	2,103	2,196	55	+83	+1	Aortic disease, liver tender, slight edema
B H	40	F	1 6	3,200	3 024	176	1,953	1,816	39	107	5 1	No evidence of decompensation
P R	45	M	1 58	3,070	3,732	217	1,911	2,086	52	+175	+9	Fibrillation, no edema
F G	45	M	1 57	3,925	3,715	210	3,038	3,757	0	181	1 6	Aneurysm of aorta
M O	44	M	1 62	1,050	3,827	223	2,750	2,750	32	0	0	Chronic bronchitis, emphysema, asthma
Mrs T	43(?)	F	1 5	3,000	2,835	165	965	1,310	70	+435	+18	Diminution in vital capacity due to syringomyelia, no rales, cough or fever
E O	23	F	1 54	3,050	2,911	139	1,700	1,650	45	50	3	Patient had no cause for increased metabolic rate, could do nothing but lie quiet
S M	13	M	1 32	3,300	3,118	182	2,396	2,086	28	310	12	Moderate dilatation of right auricle, aortic and mitral, acute rheumatic fever
Mrs B	45	F	1 6	3,200	3,024	176	2,152	1,890	23	262	12	Hyperpnea, no particular orthopnea, acute endocarditis and nephritis
O M	52	M	1 7	3,825	3,624	210	3,179	2,961	20	218	6 8	Mitral disease, fibrillation, no edema
L P	43	M	1 71	4,275	4,039	235	3,543	3,328	18	215	6	Slight edema, fibrillation
S M	26	M	1 83	3,050	3,732	217	3,982	3,938	0	44	1	No edema, no moisture at bases
J V	21	F	1 35	2,700	2,551	148	2,196	2,196	20	0	0	No edema, mitral disease, slight endocarditis, no decompensation
J W	26	M	1 96	4,900	4,630	270	5,201	4,855	0	316	6 6	Endocarditis, heart trouble, no disease
A R	37	M	1 64	4,100	3,875	225	3,436	3,137	16	299	8 7	Complaint, heart trouble, no disease
S R	25	M	1 75	4,375	4,124	241	3,938	3,734	10	204	5 1	Endocarditis, no signs of failure
L D	18	F	1 4	2,800	2,642	158	993	971	65	22	2	No decompensation, mitral insufficiency
												Chronic endocarditis, no decompensation, most of loss of vital capacity due to old paralysis as result of anterior poliomyelitis involving respiratory muscles

\* Inasmuch as we have no normal standards for older people in the case of those over 45 years of age we deduct 10 per cent from our normal standards, which were obtained from people from 20 to 30 years of age. We believe that this amount of reduction due to age would be approximately correct.

reduced because of an extensive syringomyelia involving her respiratory muscles, which prevented her from sitting up with ease. The reduction of her vital capacity must have been due to this cause, as her heart and lungs were normal.

In the case of L. D., Table 3, the results were totaled in our averages, but we believe much of the loss of her vital capacity was owing to an old paralysis as result of anterior poliomyelitis involving her respiratory muscles rather than to her heart disease.

Finally, Table 4 shows the whole of our series of forty-two patients grouped under what we believe to be their proper classifications and averages. The greatest vital capacity shown by any patient with

TABLE 4—AVERAGE OF ALL RESULTS ON PATIENTS

	Number of Cases Studied	Average Estimated Normal Vital Capacity of all Patients Studied Sitting, Cc	Average Actual Determined Vital Capacity of all Patients Studied Sitting, Cc	Average Per- centage Reduction of the Vital Capacity as a Result of Disease	Average Loss in Cc of of the Actual Vital Capacity by Lying Down	Percentage Loss of the Actual Vital Capacity by Lying Down	
Orthopnea of necessity	9	3,939	1,222	69.4	327	26.7	All of these patients fall within our group of the 80% or more of normals who lose a varying degree of their vital capacity on lying down.
Orthopnea of choice	14	3,746	1,753	54+	219	12.5	All of these patients fall in the same 80% group.
Patients with great reductions of the vital capacity without orthopnea	19	3,757	2,696	36	127	4.7	18.5% of these patients fall into the 20% group or thereabout of normal individuals who increase their vital capacity or do not lose any on lying down.

"orthopnea of necessity" (Table 1) was 1,213 cc, or a 58 per cent reduction from his estimated normal. The least was 1,107 cc, or a 78 per cent reduction from the estimated normal, and this latter case was clinically the most severe instance of orthopnea we have encountered. All cases of "orthopnea of necessity" had an average reduction of 69.5 per cent from their estimated normal as a result of disease, and on lying down they lost 26.7 per cent in addition, or one-fourth of their then greatly reduced vital capacity. The cases classified as "orthopnea of choice" (Table 2) showed an average reduction of 55 per cent, due to disease, and they lost on lying down an average of 12.5 per cent, or one-eighth of their reduced vital capacity. The group in Table 3 showed varying degrees of loss of

vital capacity from disease. None of these patients had orthopnea. They had an average reduction in vital capacity of 36 per cent of the estimated normal, and lost only an additional 4.7 per cent on lying down.

We have data on about twenty additional cases which for various reasons are not included in this report, but they would not materially alter the results herein recorded. We propose to go forward with the work, and the cases which we now have will form a part of our third contribution on this subject.

The subject matter in our former paper and this one has entailed many figures and much calculating. We have tried to eliminate all errors in totals, but doubtless some small ones have crept in. However, they would in no way invalidate our results.

#### SUMMARY

1. We conclude from our results that orthopnea can be divided into orthopnea of necessity and orthopnea of choice.

2. Orthopnea cannot exist without reduction of the vital capacity. If the original loss from disease is great and the patient loses an additional amount on lying down, as did 80 per cent of our normals, there will be "orthopnea of necessity." "Orthopnea of choice" is more common and exists when the original loss from disease is smaller or the percentile loss, as a result of posture, is not so great.

Some patients with as great reduction in their vital capacity from disease as is seen in "orthopnea of necessity" do not become orthopneic. We believe them to be like the 20 per cent among our 290 normal subjects whose vital capacity was unchanged or increased when they lay down.

We desire to express our thanks to Miss Ruth Trump, our chemical assistant, and Mr. E. J. Warnick, our chief technician, for valuable aid in compiling the data in this paper and our previous one.

# THE EFFECT OF OLIVE OIL ON GASTRIC FUNCTION AS MEASURED BY FRACTIONAL ANALYSIS \*

BRUCE C LOCKWOOD, M D  
AND  
HAZEN G CHAMBERLIN, M D  
DETROIT

Olive oil is not uncommonly used in hypersecretory gastric disorders. Most textbooks mention olive oil and infer that its administration lessens the secretion and delays gastric evacuation. References, however, as to proof of its action are few.

Cowie and Munson,<sup>1</sup> in 1908, made an extensive and convincing report on its action. Pawlow, working on dogs, first found that olive oil did not stimulate gastric secretion but actually delayed it. Similarly, on man after the ordinary testmeal extracted at one hour, and after meals with portions extracted at frequent intervals it has been found that olive oil and cotton seed oil when given before meals lessened acidity, delayed the height of secretion and retarded evacuation, while when given after meals it only delayed the height of secretion. These investigators believed its action to be due to coating both the food and mucous membrane, thereby lessening the usual reflex local action of the food on secretion and peristalsis.

Crohn<sup>2</sup> recently reported two observations on the effect of olive oil on the fractional curve. In the first case 2 ounces of olive oil were given immediately after the testmeal and a greater acidity was observed than in the control curve, while the emptying time remained the same. His second observation was made in a case of continual hypersecretion in which 3 ounces of olive oil were given half an hour after the test meal and a diminution of average total acidity from 101.5 to 81.6 degrees was noted. He states that he was disappointed in its action. Two observations, however, are quite insufficient to form any conclusion, especially in view of the variability of the stomach response at different times to the same stimulus.

We have noted clinically that most patients with hypersecretion report improvement after taking olive oil, yet occasionally one is found who does not seem to take the oil well, and complains of increased distress, regurgitation, etc.

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1 Cowie, D. M., and Munson, J. F. An Experimental Study of the Action of Oil on Gastric Acidity and Motility, *Arch. Int. Med.* **1**: 61 (Jan.) 1908.

2 Crohn, B. B. Studies in Fractional Gastric Analysis, *Am. J. M. Sc.* **155**: 801 (June) 1918.

We have observed thirteen patients, seven of whom were considered to have a normal gastro-intestinal tract and six had been found to have an ulcer, either, pyloric or duodenal

*Procedure*—The patient with a morning fasting stomach swallowed the small fractional tube and the fasting contents were aspirated. An Ewald meal was then given with the tube left in place and from 5 to 10 c c of contents was aspirated at definite intervals until the return was consistently free of bread. There was noted in each specimen the presence or absence of bread and bile. The free and total acidity was determined by the Toepfer method. All patients were tube broken before securing a control curve, and an effort was made to have them continue on about the same intake of food and water. Within one or two days after securing the control curve another curve was obtained under the same conditions, except that one ounce of olive oil was given

TABLE 1—SHOWS THE RESULTS IN SEVEN NORMAL CASES FROM ADMINISTRATION OF 1 OUNCE OLIVE OIL FIFTEEN MINUTES BEFORE EWALD MEAL

Case	Average Free HCl		Average Total Acidity		Maximal Free HCl		Maximal Total Acidity		Evacuation Time			Bile	
	Con- trol	Curve after	Con- trol	Curve after	Con- trol	Curve after	Con- trol	Curve after	Con- trol	After	Oil	Con- trol	Oil
	Curve	Oil	Curve	Oil	Curve	Oil	Curve	Oil	Bread	Bread			
A D	40	30.5	52	45.7	51	50	66	65	120	180	180+	0	+
A L	26.4	17	50.4	29.1	35	34	54	44	100	200	200+	0	+
J M	37	27.1	54.2	36.5	56	42	72	55	100	120	120	0	+
P G	37.2	30.3	42	43.4	63	44	70	52	120	200	200+	0	+
G S	36	36.0	54	46.4	60	52	80	60	80	180	210+	0	+
H M	46.2	26.4	66.6	43.1	83	63	98	70	75	105	135	0	0
J K	0	0	19	19	0	0	30	35	90	75	100	0	+
Aver	37.1	27.9	48.3	39.0	58.0	49.1	67.1	54.4	97.8	151.4	163.5		

after the aspiration of the fasting contents and fifteen minutes previous to the Ewald meal. In the specimens of the test curve the presence of olive oil was also noted and an effort made to determine its evacuation time. In more than one half the tests oil was still present in the stomach for a considerable period after the bread had disappeared and the experiment was discontinued.

*Results*—In Table 1 are tabulated the results in the seven normal cases observed. As will be noted, the average free acidity was reduced 9.2 degrees after taking the oil and in only one case was the average free acidity as high after taking oil as it was in the control.

The average total acidity was reduced about the same amount (9.3 degrees). In one case it was slightly higher after the oil and in another, an achylia, the average total acidity remained the same.

The high point of free acidity was reduced 8.9 degrees and of total acidity 12.7 degrees. In no case did the maximal free acidity go as high after taking oil as in the control curve, yet in one case the high point of total acidity was slightly higher with oil than without it.

The evacuation time in the controls averaged 97.8 minutes while after oil administration the average stay of bread in the stomach averaged 151.4 minutes, a delay of 53.6 minutes. Oil was still present in the stomach in four of the seven cases for an average time of 163.5 minutes, that is, in the majority of cases it was still present 10 minutes after the bread had left, showing that it is the last to be evacuated by the normal stomach.

Bile regurgitation was not seen in any of the seven control curves, yet in the oil test curves it was observed in one or more specimens in six of the experiments. Figure 1 shows the curves of total acidity representing about the average results seen in this series.

Table 2 shows the results of six observations made on ulcer cases. The average free acidity was lowered 11.6 degrees. However, in one observation (M. G. 2) it was 13.6 degrees higher after taking oil than in the control test.

TABLE 2 — SHOWS THE RESULTS IN SIX CASES DIAGNOSED DUODENAL OR GASTRIC ULCER FROM ADMINISTRATION OF 1 OUNCE OLIVE OIL FIFTEEN MINUTES BEFORE EWALD MEAL

Case	Average Free HCl		Average Total Acidity		Maximal Free HCl		Maximal Total Acidity		Evacuation Time			Bile	
	Con- trol	Curve after	Con- trol	Curve after	Con- trol	Curve after	Con- trol	Curve after	Con- trol	After	Oil	Con- trol	Oil
	Curve	Oil	Curve	Oil	Curve	Oil	Curve	Oil	Bread	Bread			
M. X.	63.5	50	75	64.5	93	76	110	82	135	180	180	0	+
A. H.	58.2	39.8	66.7	77.8	108	55	140	92	135	180	180+	+	+
H. S.	58.2	44.8	74	59.9	80	62	98	85	120	120	165+	0	0
M. S.	85.8	50.2	96	69	85	80	98	123	105	135	180+	+	+
H. G. <sup>1</sup>	51.2	49.4	67.7	65.5	58	70	78	93	105	135	135	0	+
H. G. <sup>2</sup>	45.4	59	65.1	81	72	87	98	108	135	180	210	0	0
Aver.	60.4	48.8	74.0	69.6	82	71	102.8	97	123	160	175		

The average total acidity was reduced only 4.4 degrees and ran higher in two cases after oil administration.

The maximal free acidity was reduced 11 degrees, yet in two observations (M. G. 1 and M. G. 2) the peak of the curve was higher after taking oil.

The maximal total acidity was lowered 5.8 degrees yet in three of the tests the high point after taking oil exceeded the control curve.

The average evacuation time of the bread in the control tests was 123 minutes, after taking oil it was 160 minutes, and the oil still remained in the stomach from fifteen to twenty minutes later in one half the cases.

Bile regurgitation was noted in two of the control curves and in four of the six test curves.

In Figure 2 are shown the curves of total acidity before and after oil administration as observed in patient H. S. This represents the average affect of oil.

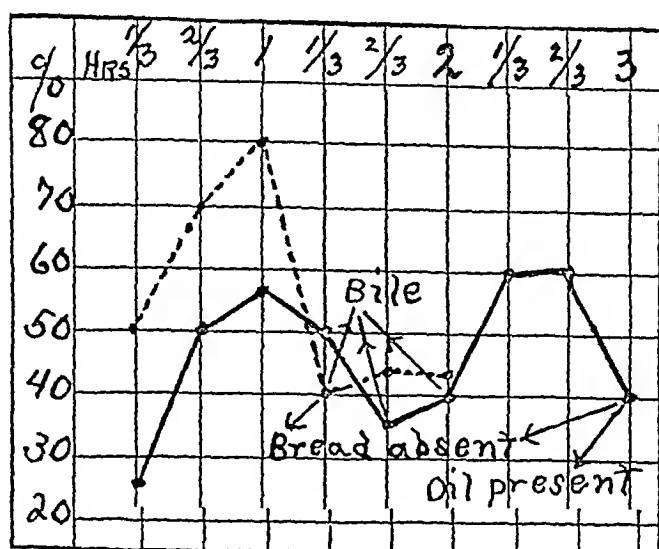


Fig 1—Curves of total acidity in the case of G S representing average results. Dotted line, control curve, solid line, curve after taking oil.

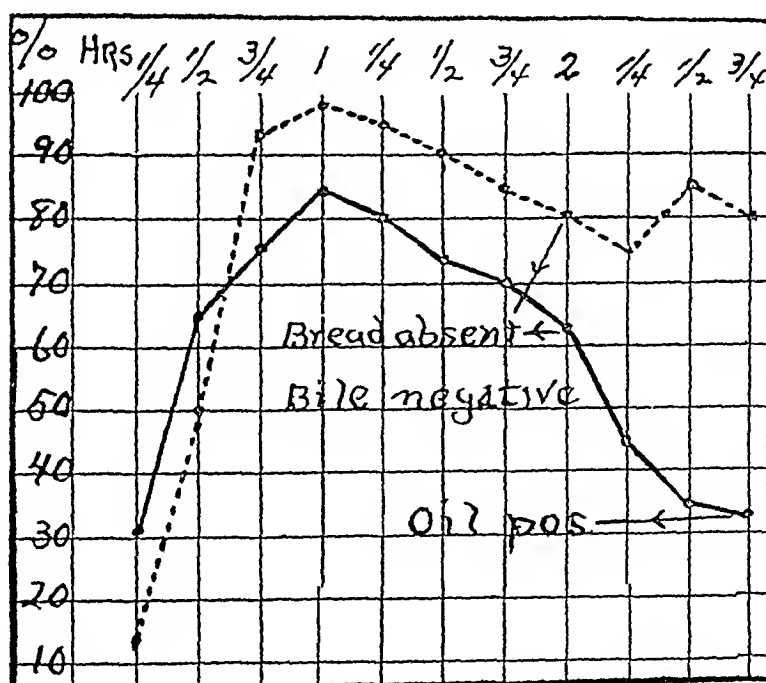


Fig 2—Curves of total acidity before and after taking olive oil as observed in H S. Dotted line, control curve, solid line, curve after taking oil.



In the whole series of thirteen observations, the average free acidity was reduced 9.5 degrees, and in only one of the thirteen cases was it higher after taking oil than before. The average total acidity was reduced 7.8 degrees, and in only three of the thirteen cases was it higher after taking oil. The high point in the curves of free acidity was reduced an average of 10.8 degrees and was higher in only two cases after taking the oil than in the control. The high point of total acidity was reduced an average of 9.1 degrees, yet in four of the cases it ran to a higher point after the administration of the oil. The evacuation time for the bread of the Ewald meal was lengthened about forty minutes, and the oil remained in the stomach an average of at least fifteen minutes longer. Bile regurgitation occurred in ten cases after the use of oil, and in two of the normal controls.

There was no marked difference between the results in normal cases and ulcer cases, except possibly the oil action was slightly greater in the former than in the latter.

#### SUMMARY

These experiments demonstrate that olive oil given before meals, as is usually done clinically, reduces the average total acidity about 12 per cent, and lowers the high point of the curve about the same degree. It causes a marked delay of the test meal in the stomach and the oil is the last portion of the meal to be evacuated. When oil is given, regurgitation of bile is five times as frequent as without it.

A discussion of the mechanism by which these effects are produced would involve a lengthy discussion of gastric physiology. Our results are similar to those obtained by Cowie and Munson, who attributed the oil action to coating of the food and mucous membrane whereby the usual local reflex action of the food is lessened.

In view of the marked biliary regurgitation (present in ten cases out of thirteen cases following oil administration) it may be well to consider this among the causative factors in our findings.

The presence of bile in the stomach usually means reverse peristalsis. This alone might account for the delay in emptying time. Alkaline duodenal regurgitation might also lower the acidity to the extent found.

Spencer, Meyer, Rehfuess and Hawk<sup>3</sup> believe that duodenal regurgitation is a body defense to protect the small intestine from oncoming irritants. They found trypsin almost constant in the stomach and it was not necessarily accompanied by bile. The higher the trypsin content the lower the acid level. This self regulating action of the pylorus has also been emphasized by Boldyruff<sup>4</sup>.

<sup>3</sup> Spencer, Meyer, Rehfuess and Hawk. Effect of Duodenal Regurgitation on Gastric Function, *Am J Physiol* 39 459, 1916.

<sup>4</sup> Boldyruff, W. The Self-Regulation of the Acidity of the Contents of the Stomach, *Quart J Exper Physiol* 8 1, 1914.

## CONCLUSION

The administration of 1 ounce of olive oil before meals causes a reduction of the average acidity and a lowering of the high point of acidity about 12 per cent. It also causes a delayed evacuation for the bread of an Ewald meal for forty minutes longer than in the control and the oil remains at least fifteen minutes longer. It also causes a regurgitation of bile in about 80 per cent of cases.

# STUDY IN BASAL METABOLISM IN DEMENTIA PRAECOX AND MANIC-DEPRESSIVE PSYCHOSES<sup>1</sup>

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The idea has long been current that disturbances of metabolism occur in certain mental disorders. Theories of an intoxication, probably endogenous, have often been advanced. Until recently the chemical methods available for clinical application did not afford sufficient evidence to indicate the extent or nature of such disturbances, and there was little to indicate what structures or functions might be involved. The more improved methods of clinical chemistry and the increasing evidence that the ductless glands are involved in many disturbances of growth and metabolism have recently caused a greatly increased interest and activity in the study of such disturbances in patients with mental disease. As a result, there is now some evidence and considerable opinion that disorders of the ductless glands and changes in metabolism may occur in certain psychopathic conditions and psychotic reactions.

Variations in the basal metabolic rate have been found to occur in clinical conditions involving certain ductless glands, especially the thyroid and pituitary. This should, therefore, be a useful method for detecting in psychotic patients disturbances of metabolism in which these glands are involved. Bowman<sup>1</sup> has obtained readings below — 10 per cent in seven of ten patients with dementia praecox. In five of the seven, the rate had increased to — 10 per cent, or higher, at the end of six months.

The observations we here report were made for the purpose of obtaining some idea as to the relation of the mental state of the patient to the basal metabolic rate, while, at the same time, we endeavored to determine in just what clinical types of psychotic reaction, studies in metabolism may be carried on most profitably and controlled appropriately.

*Technic*—The observations were made in rooms on the same floor with the ward occupied by the female patients studied. No food was given after the supper at 5.30 the evening before the tests, and the samples were collected from 9.15 to 11 a. m. The female patients

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<sup>1</sup> Bowman K. M., Edison, J. P., and Burladge, S. P. Biochemical Studies in Ten Cases of Dementia Praecox, Boston M. & S. J. **187** 358, 1922.

were kept in bed on the morning of the test, taken to the toilet at 8 30 and then placed in large roller chairs completely recumbent and with sufficient blankets and pillows to insure comfort and warmth. They were then kept under constant observation to secure the necessary rest period and rolled into the room for observation when required. Male patients were dressed, walked down one flight of stairs, across the grounds about 200 yards and up one flight, partially undressed, and placed in the chairs at 8 30.

The apparatus used in determining the basal metabolism was a spirometer of the Tissot type having a capacity of more than 125 liters. Outdoor air was brought into the room by means of a six inch galvanized iron pipe. The inspired and expired air was separated by means of a modified Loven valve.<sup>2</sup> A gas mask,<sup>3</sup> such as was used by the French Army, was used in the majority of observations in connection with this valve and was found to be more satisfactory than the usual mouthpiece and noseclip, although in many cases both were tried. Not only did the majority of patients have less difficulty in breathing naturally through the mask, many patients almost falling asleep, but the cooperation of the patients became a less important factor so long as they remained physically quiet.

The pulse rate and respiration were counted before, during and after the observation. The average counts are recorded in the tables.

The spirometer was washed out with approximately 15 liters of expired air and the average volume expired per minute was noted. If the patient appeared fairly comfortable and seemed to be breathing naturally, the three-way valve leading to the spirometer was opened at the end of an expiration. The patient was permitted to breathe into the gasometer for six minutes unless the volume expired was abnormally small. In that case the valve was turned off at the end of an expiration after eight minutes. The time was always recorded by a stop-watch. Any physical or mental disturbance on the part of the patient was especially noted.

Samples of air were collected in bottles containing equal parts of glycerin and saturated sodium chloride solution. The expired air analyses were always done on the day of the observation, with a modification of a Henderson's air analyzer. Analyses of outside air with this apparatus gave averaged values of 0.03 per cent for carbon dioxide and 20.91 per cent for oxygen.

2 McCann, W. S. The Effect of the Ingestion of Foodstuffs on the Respiratory Exchange in Pulmonary Tuberculosis, *Arch Int Med* 25 850 (July) 1921.

3 Bailey, C. V. Apparatus Used in the Estimation of Basal Metabolism, *J Lab & Clin M* 6 657 (Sept) 1921.

In determining the values for carbon dioxide and oxygen in expired air, duplicate analyses checked within 0.04 per cent, except in two cases in which the variation was 0.05 per cent.

*Selection of Cases*—The more typical cases of dementia praecox, manic-depressive insanity and psychoneurosis were considered as most suitable, and preferably those in the more active and acute phases, provided sufficient cooperation could be had to meet the requirements of the procedure. Each patient was examined from the standpoint of disordered thyroid and other gland function. The more definite findings of this character which might influence the basal rate are noted in Tables 1, 2 and 3. Except to this extent none of the patients was considered to show gland disturbance of the recognized clinical types which would be expected to influence the rate. To what extent the readings may be accounted for in these terms will be discussed later. None of the cases was considered from routine examination to be complicated by organic disease of the nervous system or other organs except the postencephalitic case in the miscellaneous group, and a trace of albumin and a few casts in the urine, at times, in the first case in the manic-depressive group.

The cases were observed on the Psychiatric Institute Service and were carefully considered from the standpoint of clinical grouping by Dr. Geo. H. Kirby, director of the institute.

*Cooperation*—The requirements of the test are physical and mental rest and relaxation to secure a basal level. If the physical factor can be secured then variations in the mental factor can be considered in relation to the basal rate. The notes in the tables as to cooperation refer to the physical requirements, primarily the control of motor activity during the test and the preliminary rest period, and to the respiration. The term "satisfactory" designates a degree of physical cooperation comparable to that of the average nonpsychotic patient. In some cases, especially the retarded depressions, there was even less motor activity than normal. In those noted as "restless" there was some shifting or turning in the chair or moving of the head and arms, in some instances accompanied by talking. Further observations are necessary to determine just how much the rate is influenced by the motor activity and such disturbances of respiration as occur in mildly restless patients. In some of the readings the variations of this kind were considered to be so small that the reading could be classed as satisfactory. These readings are noted as satisfactory, but with the addition of notes to indicate the presence of slight variations. Less satisfactory readings are indicated by the notes. Where the reading was quite evidently influenced by motor activity the reading has been enclosed in brackets.

Mental cooperation by psychotic patients to the extent of mental quietness or relaxation in the same sense as in nonpsychotic or non-neurotic patients is of course quite difficult to obtain or even to estimate accurately. The psychic factor, the mental or emotional state or tension, in relation to the basal rate has been considered in two ways, assuming that motor activity is controlled. First, as a separate factor influencing the rate directly, and second, as a part of the total clinical picture of the psychosis. That is, whether the rate would vary with the character and intensity of the mental and emotional state at the precise time of collecting the sample, or would be more closely correlated with the clinical type of psychotic reaction as shown by the symptoms and behavior from day to day. It would now seem that the demonstration of a direct relation between the rate and the mental state at the time would require quite careful psychologic observations and a degree of cooperation which cannot be had from the types of patients who have shown the greatest variation from the normal rate. It would also probably be essential to separate the mental state into several factors including the mental content, or what the patient was thinking about, and the character and intensity of the emotional reaction both subjectively and objectively. A direct psychic or emotional influence on the rate to an extent requiring such observations at the precise time of determining the rate would suggest a considerable degree of lability and responsiveness by the rate to such stimuli. It is of interest here to note the increase in the basal rate following the subcutaneous injection of 0.5 c.c. of epinephrin,<sup>4</sup> which suggests an increased rate in primitive emotional reactions like fear, as described by Cannon and by Watson. A similar and sustained response of the organism to prolonged emotional stimuli of this kind would, however, seem more problematical. And, unfortunately, the complex emotional factor in psychotic reactions is often quite difficult of estimation and expression in these terms. In the cases here reported the consistency of consecutive readings on the same patient speaks against a responsiveness by the basal rate to any factor which can be considered separately and independently from the total clinical condition from day to day. It remains, therefore, to consider the rate in relation to the clinical reaction types into which the cases fall and what factors or symptoms in the clinical picture it can be correlated with.

#### MANIC-DEPRESSIVE GROUP

The manic-depressive cases are arranged in Table 1 somewhat according to the basal rate, with the lowest at the top. The first seven cases were typical of depression. The first four cases were recent admissions, and quite comparable clinically, had shown little or no

<sup>4</sup> Sandiford. *Am J Physiol* 51: 407, 1920

TABLE 1—MANIC-DEPRESSIVE GROUP

	Psycho motor	Emotional	Date, 1922	Basal Rate, per Cent	Cooperation	T	P	R	Weight, Lbs	Height, M	Surface Area, Ht Wt Formula (DuBois)	Volume expired Liters per Hour	Gas Analysis		Calo rics per Hour	R Q
													CO <sub>2</sub> per Cent	O <sub>2</sub> per Cent		
No 1 Depressive, male 53, Adm 1/31/22, previous attacks, 3, manic type, gradual improvement during period of these observations	Inactive, retarded, quiet	Depressed, looks distressed, no tears	2/15	-13	Satisfactory	98	60	14	147	1.77	1.82m <sup>2</sup>	292.0	3.44 3.42	16.87 16.87	59.18	0.809
			2/16	-8	Satisfactory	98	59	18	147		1.82m <sup>2</sup>	279.3	3.20 3.21	16.70 16.68	63.04	0.709*
			2/20	-15	Satisfactory	98	54	19	148		1.82m <sup>2</sup>	290.5	3.33 3.33	16.94 16.92	58.00	0.795
			3/20	-11	Satisfactory	98	54	16	145		1.81	360.1	2.76 2.75	17.60 17.56	60.19	0.752
No 2 Depressive, male 29, Adm 2/4/22, previous attacks, none, no thyroid signs, thyroid, 2 gr daily, 3/10, no improvement noted	Early active but retarded, quiet, keeps occupied in a slow way	Depressed, sad, distressed, no tears, many tears	2/24	-13	Satisfactory	98	48	15	147	1.77	1.82	403.2	2.51 2.50	17.82 17.83	62.51	0.765
			2/27	-9	Satisfactory	98	52	16	147			426.0	2.86 2.84	17.88 17.90	64.92	0.919
			3/1 thyroid	-12	Satisfactory	98	53	15	147			430.8	2.70 2.70	17.78 18.01	63.23	0.900
			3/22	-3	Satisfactory	98	48	20	149			468.5	2.56 2.56	17.96 17.96	69.74	0.826
No 3 Depressive, female 57, Adm 3/11/22, previous attacks, 2	Inactive retarded, quiet	Depressed few tears	3/21	-11	Satisfactory	98*	88	11.19 irreg	161.5	1.64	1.79	348.1	2.45 2.45	17.69 17.73	55.79	0.714*
			3/25	-11	Satisfactory	99*	82	17	162.5			364.3	2.40 2.41	17.86 17.89	55.48	0.744
			2/21	-9	Satisfactory	98	72	12	125	1.65	1.61	309.6	2.85 2.84	17.52 17.49	52.82	0.796
			2/23	-15	Satisfactory	98.4	72	11	125		1.61	272.0	3.00 3.00	17.35 17.33	48.81	0.798
No 4 Depressive, female 45, Adm 1/19/22, previous attacks, 3, skin dry, glossy, yellowish, thin, hair dry, brows thin, thyroid, 2 gr daily 3/12, no definite improvement noted	Inactive, retarded, wants to stay in bed	Depressed sad expresses but smiles feebly at times, no tears	3/2 thyroid	-8	Satisfactory	98.2	66	15	123		1.60	307.9	2.79 2.79	17.49 17.48	52.78	0.771
			3/21	-2	Satisfactory	98	60	15	123.5		1.60	319.1	2.95 2.94	17.39 17.42	56.17	0.800
			3/29	-6	Moved several times, after in ask was removed cried and said she was afraid	98	60	16	127	1.68	1.64	357.9	2.69 2.70	17.80 17.77	56.32	0.823
No 5 Depressive, female 38, Adm 3/27/22, previous attacks, 2	Inactive	Depressed, suicidal	2/2	-6	Satisfactory	98.8	63	12	149.5	1.79	1.84	323.7	3.78 3.76	16.82 16.84	66.48	0.808
			2/6	-3	Satisfactory	98.2	62	10	151		1.84	346.4	3.69 3.67	16.93 16.94	69.18	0.902
			2/7	-6	Satisfactory	98.4	84	16	86.5	1.59	1.34	259.4	3.13 3.11	16.94 16.97	45.28	0.743
			2/11	+3	Satisfactory	98.2	78	16	88		1.35	272.4	3.21 3.16	17.23 17.26	50.08	0.835
No 6 Depressive, male 41, Adm 1/26/22, previous attacks, 1, manic type, improved since adm	Inactive, quiet, slightly retarded	Depressed stolid expression, no tears	2/2	-6	Satisfactory	98.8	63	12	149.5	1.79	1.84	323.7	3.78 3.76	16.82 16.84	66.48	0.808
			2/6	-3	Satisfactory	98.2	62	10	151		1.84	346.4	3.69 3.67	16.93 16.94	69.18	0.902
			2/7	-6	Satisfactory	98.4	84	16	86.5	1.59	1.34	259.4	3.13 3.11	16.94 16.97	45.28	0.743
			2/11	+3	Satisfactory	98.2	78	16	88		1.35	272.4	3.21 3.16	17.23 17.26	50.08	0.835
No 7 Depressive, post partum, female 41, Adm 9/24/21, previous attacks, 2 each postpartum, now much improved, underweight 15 pounds, but gaining	Inactive, quiet	Depressed, unstable, smiles easily at times	2/2	-6	Satisfactory	98.8	63	12	149.5	1.79	1.84	323.7	3.78 3.76	16.82 16.84	66.48	0.808
			2/6	-3	Satisfactory	98.2	62	10	151		1.84	346.4	3.69 3.67	16.93 16.94	69.18	0.902
			2/7	-6	Satisfactory	98.4	84	16	86.5	1.59	1.34	259.4	3.13 3.11	16.94 16.97	45.28	0.743
			2/11	+3	Satisfactory	98.2	78	16	88		1.35	272.4	3.21 3.16	17.23 17.26	50.08	0.835





TABLE 2--DEMENTIA PRAECOX GROUP

Date, 1922	Basal Rate, per Cent	Cooperation	T	P	R	Weight, Lbs	Height, M	Surface Area Ht-Wt Formula (DuBois)	Volume Expired Liters per Hour	Gas Analysis		Calo ries per Hour	R Q
										CO <sub>2</sub> Cent	O <sub>2</sub> Cent		
No 16 Male 17, Adm 2/4/22 depressive delusional, quiet, apprehensive, fearful, soon after becoming actively suicidal on delusional basis, requiring restraint and constant watching, slightly emaciated, pale, Hgb 85%, history of very rapid growth	2/10 -25 2/14 -32 2/15 -24	Satisfactory, apprehensive and nervous Satisfactory, somewhat apprehensive Satisfactory, apprehensive	98 98 98	76 60 66	19 21 19	90 90 91	1 64	1 40m <sup>2</sup>	211 2 220 0 226 3	3 25 3 26 3 09 3 08 3 40 3 38	16 65 16 62 17 21 17 22 16 87 16 87	45 10 40 74 45 85	0 72 0 792 0 798
No 17 Female 16, Adm 10/28/20, catatonie type, usually mute, wets and soils at times, eats ravenously, well nourished, childish appearance, sex development retarded, has menstruated only one time, thyroid full, possibly slightly enlarged, Pulse 120 130 at times	2/ 3 (+ 9) 2/ 9 -17 2/11 -23	Not satisfactory, tried to sit up Satisfactory Satisfactory	99 98 98 98	112 96 84	16 16 15	91 90 5 88 4	1 59	1 37	369 6 286 9 286 5	2 80 2 79 2 63 2 63 2 95 2 94	17 28 17 28 17 73 17 74 17 38 17 41	59 79 45 55 41 72	0 722 0 787 0 797
No 18 Female 19, Adm 1/31/22, hebephrenic type, childish appearance, wets and soils bed wetter for past two years, profane, thyroid slightly and uniformly enlarged, amenorrhea since admission	3/11 -21 3/29 (-10)	Fairly satisfactory, talked at end but volume remained constant Not satisfactory, moved constantly, talked	98 2 97 4	60 60	19 16	100 96 5	1 49	1 37 1 34	278 1 268 0	2 64 2 64 2 76 2 77	17 99 18 01 17 47 17 49	40 7 46 06	0 877 0 761
No 19 Male 29, Adm 2/28/22, catatonie, mute, inactive, spoon fed, increased muscle tonus, prison record	3/ 6 -10 3/ 8 -17 3/23 - 5	Satisfactory Satisfactory Satisfactory	98 4 98 8 99 4	60 60 80	12 11 18 irreg	118 5 118 5 114 5	1 73	1 63 1 61	318 6 303 7 348 4	2 90 2 90 2 97 2 97 2 84 2 80	17 37 17 37 17 38 17 34 17 45 17 43	56 48 53 64 60 62	0 775 0 803 0 796
Before last reading symptoms became more pronounced, tube fed, muscle tonus greatly increased													
No 20 Female 36, Adm 2/25/21, paranoid, depressive, depressed, not definitely agitated, overactive, constantly at work	3/14 -16	Not satisfactory, restless, afraid, crying before test, quiet 15 min before and during test	97 1	59	26	99 5	1 51	1 35	310 5	2 62	18 29	41 23	0 985

No 21 Female 26, Adm 11/9/21 paranoid type, usually quiet and in touch, perplexity, emotional lability, objective symptoms improved since admission	3/18	-13	Fairly satisfactory, apprehensive, pulse and respiration regular and normal	97.1	48	18	97		1.36	2467	279 277	17.40 17.42	43.17	0.747
	2/3	-16	Fairly satisfactory, quiet, uneasy, wanted to hold breath	98.2	50	12	97	1.61	1.42	192.5	3.75 3.77	16.31 16.34	44.11	0.779
	2/9	(+ 9)	Not satisfactory, restless, respiration uneven	98.6	50	17	97.5			289.2	3.45 3.46	16.98 16.96	57.18	0.842
	2/10	-1	Satisfactory	98.6	72	12	97.5			287.8	2.90 2.90	17.39 17.38	50.80	0.780
	3/2	-9	Satisfactory, rest less before test	98.1	64	17	92.7		1.40	246.3	3.18 3.15	17.13 17.13	46.72	0.798
No 22 Male 19 Adm 2/28/22, paranoid type quiet, seclusive, apprehensive	3/6	-12	Satisfactory	99	60	20	120	1.68	1.60	391.5	2.36 2.34	17.88 17.92	59.05	0.730
	3/8	-9	Satisfactory, somewhat restless before test	99.2	68	26	118			449.3	2.17 2.17	18.27 18.28	59.30	0.751
No 23 Male 17 Adm 12/23/21 paranoid type inactive, quiet partial insight, improved since admission	3/3	-3	Satisfactory	98	72	14	129.5	1.61	1.60	336.3	3.37 3.38	17.03 17.08	65.16	0.840
	3/13	-10	Satisfactory	98.8	60	11	129.5			320.4	3.53 3.52	17.10 17.09	61.57	0.898
No 24 Male 16, Adm 9/29/21, hebephrenic type admitted after episode of excitement, improved since admission, now seclusive smiling, marked cyanosis and sweating of hands	2/6	-5	Satisfactory	98.2	76	12	119.5	1.64	1.58	277.6	4.07 4.09	16.29 16.33	64.05	0.855
	2/10	-9	Satisfactory	98	72	17	122			291.5	3.65 3.69	16.61 16.66	62.21	0.819
No 25 Male 23, Adm 5/1/21, paranoid type, overactive, euphoric psychopathic, criminal history	2/15	+12	Fairly satisfactory, quiet uneasy, fingers moved constantly during test	98	80	13	114.5	1.66	1.56	284.3	4.28 4.28	16.07 16.08	68.87	0.854
No 26 Male 21, Adm 1/7/22, paranoid type, periods of overactivity and excitement, first reading followed and last reading just preceded these disturbed periods	2/2	+16	Satisfactory	98.2	81	16	123	1.68	1.62	342.6	3.40 3.43	16.60 16.59	73.82	0.747
	2/8	+11	Satisfactory	98	74	15	122		1.61	304.3	3.77 3.77	16.25 16.27	70.62	0.768
	3/15	+17	Satisfactory	98	79	18	115		1.58	435.7	2.84 2.84	17.54 17.58	73.29	0.807

improvement when these observations were started, cooperated well, and showed rather consistent readings which averaged — 11.2 per cent. The fifth patient did not cooperate well. The sixth and seventh patients were much improved and showed readings more nearly normal. In Case 9 the manic attack was accompanied by considerable loss of weight. The first readings, — 8 and — 15 per cent, respectively, were made soon after the patient was quiet enough to cooperate. There was rapid improvement with gain in weight. The last readings were made just as the patient was ready to go home, and were + 7 and + 5 per cent respectively.

In Case 15 there were no very definite signs of hyperthyroidism, although the readings were + 35 and + 20 per cent. Since admission the emotional reaction has been objectively quite marked. At first she cried easily and showed a flushed face, and is now quite definitely and genuinely elated.

Two patients (Cases 13 and 14) showed the agitated type of depression, but cooperated sufficiently well to indicate that their agitation did not raise the rate above the normal limits, although it may have kept it from being as low as in the simple depressions.

In the manic-depressive table there has been set out in separate columns a rough estimate of the psychomotor and emotional factors in the clinical picture as shown from day to day. Study of these in relation to the rate indicates that further observations are necessary to determine whether any very close relation exists between these factors and the basal rate, and that one cannot be considered without the other. In addition to the question of cooperating, it should also be borne in mind that a hypomanic state may represent a transient or rather convalescent phase of the psychosis, and for this reason may not be comparable to the more marked manic or depressed states. Gains in weight have been noted in some such cases.

If, as is indicated by these findings, the rate is slightly decreased in depressions, it should probably not be concluded that the basal rate is influenced in the same way in individuals suffering from emotional disturbances but who have not become psychotic. Many of these manic-depressive attacks seem to be clearly precipitated by emotional and other influences similar to those found in the history of many cases of exophthalmic goiter, while in others it is apparently impossible to establish a relation between an emotional disturbing cause and the mental break-down.

#### DEMENTIA PRAECOX GROUP

Cases which were considered to be essentially and fundamentally of the schizophrenic type have been included in Table 2. As previously

indicated, there was not enough evidence of disturbed endocrine function to explain these definitely abnormal rates in terms of recognized clinical types, i. e., as hypothyroid or hyperthyroid or pituitary. Skin evidence of myxedema was not found in any case in this group. There was no adiposity nor definite infantilism. Evidence of growth disturbance was, however, present in some. One patient (Case 16) gave a history of recent very rapid growth. Another (Case 17) had not attained physical sex maturity and had had a single scanty menstruation. One (Case 18) would probably be classed as polyglandular. None of the males was very definitely deficient in gross gonadal development, and in most of them, including Case 16, it was equal to the adult average. Several patients showed deficient or perverse secondary sex features. In the light of present evidence these lesser degrees of disturbed development of bone, muscle, and the physical characteristics of sex probably cannot be expressed in terms of any one gland. Adequate function of several glands seems to be necessary for complete physical maturity. Therefore, the most that can be said as to their relation to metabolism is that some of the cases show this much evidence of a disturbance of an "endocrine" nature. Some evidence as to the frequency of imperfect and retarded sex development in cases with early onset will be presented by one of us (Gibbs) in another paper.

Starvation or undernutrition does not seem to explain the findings except possibly to some extent in Cases 16 and 19. These patients were poorly nourished and there was some question of restriction of food intake due to an inclination to refuse food. The extent of this could not be determined. None of the others was definitely undernourished. One patient (Case 17) had required to be spoon-fed when admitted in 1920 but for several months had eaten ravenously her own food and that of other patients and was well nourished.

One boy (Case 16) presented several features which suggested a more profound disturbance of metabolism than simple inanition as the cause of the low readings, which averaged -27 per cent. In October, 1920, soon after the patient was 16 years of age, this boy had left his position and found work elsewhere because he thought the girls in the office where he worked were laughing at him. Later he felt too weak to work, and finally in August 1921, he quit work entirely, and definite ideas of reference were noted. Fear was said by his mother to be a dominating symptom for a year before his admission. After September, 1921, he would not leave the house and was very fearful. In October, 1921, he began to grow so rapidly as to require new clothing. This was associated with a voracious appetite, especially for sweets. About Christmas 1921, severe headaches developed, appetite became poor and bowels constipated. This continued until February when an acute delusional episode with an attempt at suicide caused admission to the hospital, Feb. 4, 1922.

He was thin, and the muscular wasting, or lack of development, seemed slightly out of proportion to the loss of subcutaneous fat. The thyroid was palpable at the isthmus, but was thought to be small. There was no appearance of myxedema. The testes were of the average adult size with a fair growth

of pubic hair of masculine type No hair on chest or face Had to be spoon-fed Said he could not eat because bowels were stopped up and stomach was full Bowels moved daily voluntarily or by enema This was the status when the basal rate determinations were made There was no loss of weight during the five days between the first and last determinations February 21 a twenty-four hour urine of 1,250 c c contained 3 gm creatinin and 387 mg creatin (Folin method, creatinin-zinc chlorid standard) March 2 a twenty-four hour urine of 1,015 c c contained 1 349 gm creatinin and 172 mg creatin with a total nitrogen of 7 32 gm (Kjeldahl) February 17 the fasting blood sugar was 112 4 mg per 100 c c (Folin), and forty-five minutes after the ingestion of 80 gm of glucose it had risen to 230 mg Sugar did not appear in the urine (Benedict)

Further observations could not be made because the patient became so actively suicidal in response to his delusions as to require constant restraint in a protection sheet Thyroid, 2 grains daily, was given from March 9 to March 19, but produced no appreciable effect and was discontinued because of a loss in weight Restraint continued to be necessary April 15 the hands and forearms were markedly cyanotic and cold, and passive motion at the elbows was difficult because of greatly increased muscle tonus Tube fed twice daily Anterior pituitary (Armour),  $\frac{1}{4}$  grain daily, with one of the meals was begun, since which time gradual increase in food intake with gain in weight has been noted May 5 he was taking his food voluntarily, muscular tension has relaxed and cyanosis almost gone

The cases are too few to attempt correlations between the rate and the clinical picture as a whole or separate symptoms or factors Just how much the rate varies with the clinical picture, with the quiet and disturbed phases, the fluctuations in weight, appetite, and behavior which some of these patients show must be the subject of further careful observations, following the same patient through these changes In the cases studied those which seemed to be in the more active or acute phases of the reaction also showed the greatest variation from the normal rate In Case 19, however, it was noted that with an increase in the severity of symptoms, the rate became more nearly normal Two factors may have influenced it, the greatly increased muscle tonus or the increased protein in the tube-fed meals of milk and eggs which the patient had been receiving for three days before the last reading

Correlation between the basal rate and the psychomotor and emotional factors has not been attempted in this group, since they are in many cases so much more difficult of description, evaluation, and classification than in the affective group In certain of the dementia praecox cases with a definite emotional coloring the basal rate showed quite definite variations from normal In Case 16 there was marked depression and apprehension on a delusional basis, while in Case 26 there were periods of excitement and over-activity and an increased rate just following and preceding such periods In other cases however (Cases 17 and 18), the emotional factor was not prominent, and there were also definitely low readings

## MISCELLANEOUS AND CONTROL GROUP

Case 27 was not included in the dementia praecox group because some doubt remains as to the essential nature of the psychosis. The patient recovered from the first episode with apparently complete insight. The diagnoses made at the time are indicated in Table 3. The clinical picture at the time the readings were made was one of depression. The readings were lower than in the simple depressions and the rate was not raised by thyroid, suggesting the possible presence of some constitutional factor not present in the simple depressions.

There is also some question as to the diagnosis of cases classed as psychoneurosis. They have been introduced as control cases for the reason that they were in a settled chronic state rather than an acute phase of their psychosis. Cases of psychoneurosis which would afford a satisfactory basis for comparison with neurotic types usually regarded as nonpsychotic were not available in the hospital at the time these observations were made.

Three nurses and one physician who served as controls gave normal readings, while one nurse and one physician gave abnormal readings, the evidence for which is shown in the tables.

The discussion in this paper has probably gone into more detail than is warranted by the data. It may be justified by bringing out some of the points to be considered, especially that in functional studies of this character interpretation of the findings must be made in the light of the clinical state or phase presented by the patient at the time. Some of the reports on biochemical studies in the functional psychoses indicate that this has not always been considered. The work of Folin<sup>5</sup> on metabolism in mental disorders has been subjected to this criticism by Pighini and Statuti.<sup>6</sup> It is of interest to note that while the work of Folin was quite exhaustive on the chemical side, the selection of cases and limited clinical observations prevented correlations between the chemical findings and the acute and chronic phases. The seven dementia praecox cases studied were all in the chronic phase. If there are abnormal variations in the metabolism in dementia praecox it would seem probable that such changes would be most marked and therefore most tangible and appropriate for study in the more active and acute phases of the process. Pighini and Statuti found an excessive elimination of nitrogen, phosphorus, and unoxidated sulphur in all of six cases of dementia praecox in an acute exacerbation. Benedict<sup>7</sup> recently suggested a close relation between nitrogen loss and decreased basal rate.

5 Folin. *Am J Insanity* **60** 699, 1904, **61** 299, 1904

6 Pighini and Statuti. *Metabolism in Dementia Praecox*, *Am J Insanity* **67** 299, 1910

7 Benedict. *Metabolism During Starvation and Undernutrition*, New York M. J. **115** 249 (March) 1922

TABLE 3—MISCELLANEOUS AND CONTROL GROUP

	Date, 1922	Basal Rate, per Cent	Cooperation	T	P	R	Weight, Lbs	Height, M	Surface Area Ht.-Wt. Formula (DuBois)	Volume Expired Liters per Hour	Gas Analysis		Calo- ries per Hour	R Q
											CO <sub>2</sub> Cent	O <sub>2</sub> Cent		
No 27 Male 16, Adm 8/16/21, D P (case not clear), paroled 11/23/21, psychosis with psychopathic personality, paranoid hallucinatory episode, recovered. Returned to hospital 2/13/22, depressive, rapid growth 6 months prior to first admission, anti social behavior beginning at 13 years, fear seems to be a prominent factor, quiet, inactive	2/24	-14	Satisfactory	98	60	20	109	1.67	1.47m <sup>2</sup>	378.8	2.35 2.35	18.04 18.07	54.13	0.781
	2/27*	-19	Satisfactory	93	60	20	109.5			373.2	2.37 2.35	18.17 18.22	50.97	0.831
	3/22	-17	Satisfactory	93	52	21	104		1.44	402.8	2.25 2.26	18.39 18.36	51.29	0.859
No 28 Male 13, Adm 2/2/22, postencephalitis psychosis, overactive, talkative, adipose, some hypopituitary features, but gonadal development precocious, with feminine pubic hair	3/ 3	-20	Satisfactory	98	60	24	142	1.67	1.71	443.9	2.76 2.79	17.83 17.86	64.44	0.865
	3/13	-16	Satisfactory	99*	76	22	142			450.5	2.75 2.72	17.73 17.76	71.80	0.825
No 29 Female 28, Adm 12/19/19, psychoneurosis, anxiety type, masculine hair growth, history of pelvic operation	3/24	+ 7	Early satisfactory, restless before, quiet during test	98.8	96	14	95	1.48	1.32	291.1	2.91 2.93	17.31 17.31	52.44	0.766
	3/27	- 4	Satisfactory	98.6	84	13	95			277.0	2.71 2.69	17.53 17.53	46.63	0.756
No 30 Psychoneurosis, neurasthenic type, female 42, adm 12/31/21, previous admission, one	3/24	± 0	Satisfactory, breathing irregular	97.8	96	25	72.5	1.54	1.225	372.4	1.94 1.96	18.54 18.57	44.04	0.783
No 31 Psychoneurosis, psychasthenic type, female 41, Adm 1/20/15, masculine hair growth	3/27	- 4	Satisfactory	98.6	82	19	101.5	1.56	1.47	350.1	2.33 2.33	18.02 18.04	50.57	0.761
	3/28	- 8	Satisfactory	98.2	66	22	.			356.8	2.28 2.31	18.21 18.21	48.44	0.809
Dr H, age 27	3/20	+ 5	Satisfactory	98.4	80	11	125	1.63	1.60	397.2	2.87 2.90	17.59 17.59	66.31	0.833
Miss F, nurse, age 18	3/17	+ 4	Satisfactory	98.4	80	24	132	1.53	1.57	393.9	2.79 2.79	17.60 17.62	65.26	0.804
Miss M, nurse, age 22	3/17	+ 2	Satisfactory	98	72	20	138.2	1.56	1.61	344.5	2.89 2.88	17.42 17.40	60.51	0.781
Miss H, nurse, age 23	3/10	+ 5	Satisfactory	98.2	76	24	128.8	1.60	1.60	386.5	2.63 2.62	17.72 17.72	61.82	0.780
Miss L, nurse, age 23, several attacks tonsillitis, 20 lbs underweight, fine tremor fingers, thyroid doughy, possibly slightly enlarged	3/10	+25	Satisfactory	98.2	68	16	126.3	1.61	1.59	317.2	3.81 3.83	16.29 16.33	73.04	0.789
Dr B, age 33, adipose	3/22	-10	Satisfactory	98	80	11	181.5	1.74	1.93	369.4	3.07 3.04	17.36 17.33	65.09	0.816

\* Thyroid 2 gr daily 3/10 to 3/21

## SUMMARY

1 Definitely abnormal basal rates were found in psychotic patients in the more acute phases of their psychosis. The variations from normal were greater in dementia praecox patients than in manic-depressive insanity.

2 The patients did not show sufficient evidence to explain satisfactorily the findings in terms of thyroid or pituitary disorder. Several of the dementia praecox patients did show some evidence of disturbed growth, including incomplete sex maturity.

3 Thyroid by mouth raised the rate to normal in two cases of manic-depressive depression, but did not in a case with more marked constitutional psychopathic features. No immediate mental improvement followed thyroid in these three cases.

4 Inanition was not thought to account for the low readings except possibly to some extent in two cases. In one of these there was found a creatinin excretion of 33 mg per kilo, with 172 mg creatin, in twenty-four hours, and in the other a creatinin excretion of 26.8 mg per kilo, with 195 mg creatin, in twenty-four hours.

5 In functional studies in the psychoses the findings should be considered in relation to the symptoms and phases or stages presented by each patient as well as to the clinical group to which he belongs.



# HIPPURIC ACID SYNTHESIS AS A TEST OF RENAL FUNCTION \*

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The worth of an organ is measured by its capacity to perform the daily task, in other words, by its physiologic efficiency. This idea of the fundamental importance of the patency of the organ underlies the many attempts to discover means of assaying the functional capacity of the affected organ. The kidney, on whose integrity an individual's welfare depends to a large extent, has been the object of the greatest number of functional tests. The tests most in vogue in clinical medicine fall into several groups depending on the particular task which each purports to present to the kidney. One of the most commonly employed tests is concerned with the ability of the kidney to rid the body of a foreign body, such as the dye phenolsulphonephthalein<sup>1</sup>. Others attempt to place the kidney under an increased strain in performing its excretory function, by increasing very greatly the amount of sodium chlorid,<sup>2</sup> of uric acid<sup>3</sup> or urea<sup>4</sup> and finding out how well the kidney measures up to the expectation under the strain. Inasmuch as the kidney is an organ of considerable structural complexity, with great possibilities for compensatory rearrangement of the functional load, Mosenthal's method,<sup>5</sup> involving a survey of various aspects of the kidney physiology, comes closer, perhaps, to giving an insight into the condition of this organ than any other test, but, as was pointed out recently by Rabinowitch,<sup>6</sup> no single test is reliable and the responses to each test vary with the type of nephritis.

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1 Rowntree, L G, and Geraghty, T J. An Experimental and Clinical Study of the Functional Activity of the Kidneys by Means of Phenolsulphonephthalein, *J Pharmacol & Exper Therap* **1** 579, 1910

2 Kummer, R H. L'appréciation des fonctions renales par l'alterance des eliminations ureo-chlorurees ainsi que par le bilan chlorure au cours de la chlorurie experimentale, *Presse méd* **29** 603, 1921

3 Magath, T B. A Test for Early Renal Insufficiency, *J Lab & Clin M* **6** 463, 1921

4 MacLean, H, and de Wesselow, O L V. On the Testing of Renal Efficiency with Observations on the Urea Coefficient, *Brit J Exper M* **1** 53, 1920

5 Mosenthal, H O. Renal Functions as Measured by the Elimination of Fluids, Salts and Nitrogen, and the Specific Gravity of the Urine, *Arch Int Med* **16** 733 (Nov) 1915

6 Rabinowitch, I M. The Urea Concentration Test for Kidney Function, *Arch Int Med* **28** 827 (Dec) 1921

Ever since Bunge and Schmiedeberg<sup>7</sup> demonstrated in their experiments on dogs that hippuric acid is synthesized in the kidney from benzoic acid and glyocol, the ability of this organ to effect such conjugation has been investigated extensively as a means of determining the extent of renal injury. It stands to reason that if the hippuric acid synthesis is a specific function of the kidney parenchyma, any lesion which is sufficient to influence its functional capacity would also and, perhaps, definitely reveal itself in a diminished ability to perform the synthesis. Indeed, this consideration forms the major premise of the argument which soon after Bunge and Schmiedeberg's discovery stimulated the investigation of the hippuric acid synthesis under pathologic conditions by Jaarveld and Stokvis,<sup>8</sup> Weyl and Anrep,<sup>9</sup> and Kronecker<sup>10</sup>. These researches have helped to establish the main contention that the ability to synthesize hippuric acid suffers greatly in the human subject whose kidney parenchyma is diseased.

Recently Violle<sup>11</sup> adopted the method for clinical purposes. Realizing that quantitative knowledge of hippuric acid synthesis would throw important light on the physiologic condition of the renal organ, we decided to study this matter further in our hospital patients with primary or secondary kidney affections.

*Where Is the Hippuric Acid Synthesized?*—As was already pointed out, the quantitative study of hippuric acid excretion under pathologic conditions presupposes that the synthesis takes place in the kidney. It is immaterial if other organs or tissues are likewise potential seats of hippuric acid formation, but if these do contribute appreciably to this synthesis, then obviously there would be little justification for applying the test to estimate the renal function. In 1911, Friedmann and Tachau,<sup>12</sup> perfusing rabbit livers, found that on the addition of benzoic acid, the perfusion blood contained hippuric acid. They advanced the view that in the herbivorous animal, at any rate, the liver partakes in the synthesis. Their method of analysis, however, is quite involved and by no means quantitative (*Die beschriebene Method ist keine quantitative*). They found that only a limited synthesis occurs, and,

7 Bunge, G., and Schmiedeberg, O. Ueber die Bildung der Hippursäure, *Arch exper Pathol u Pharmacol* **6** 233, 1876.

8 Jaarveld, G. J., and Stokvis, B. J. Ueber den Einfluss von Nierenaffectionen auf die Bildung von Hippursäure, *Arch exper Pathol u Pharmacol* **10** 268, 1879.

9 Weyl, T., and Anrep, B. Ueber die Ausscheidung der Hippursäure und Benzoesäure während des Fiebers, *Ztschr f physiol Chem* **4** 169, 1880.

10 Kronecker, F. Ueber die Hippursäurebildung beim Menschen in Krankheiten, *Arch exper Pathol u Pharmacol* **16** 344, 1883.

11 Violle, P. L. Recherches sur "l'épreuve de la synthèse hippurique" comme moyen d'exploration des fonctions rénales, *Ann de méd* **9** 330, 1921.

12 Friedmann, E., and Tachau, H. Ueber die Bildung des Glykokolls im Tierkörper. I. Synthese der Hippursäure in der Kaninchenleber, *Biochem Ztschr* **35** 88, 1911.

a very significant finding, that the addition of glycol to the perfusion blood did not increase the hippuric acid output. In view of this fact, and also because their perfusion experiments with kidneys failed to yield any hippuric acid, the results of Friedmann and Tachau do not seem to us to establish a *prima facie* case for the hypothesis that the liver participates to an important degree in the synthesis. Of course, these authors, having recognized the convincing force of Bunge and Schmiedeberg's experiments, suggested that a fundamental difference exists between herbivorous and carnivorous animals as far as hippuric acid synthesis is concerned. Kingsbury and Bell,<sup>13</sup> however, found relatively large amounts of hippuric acid in the blood and liver of nephrectomized dogs following an injection of sodium benzoate and glycol. These experiments seemed to break down the demarcation between herbivorous and carnivorous animals which Friedmann and Tachau's studies suggested, and to reinforce the hypothesis that hippuric acid synthesis is a generalized function of the organism. It must not be overlooked, however, that the living organism possesses great compensatory ability. Kingsbury and Bell's experiments on dogs with both kidneys removed really prove nothing beyond the fact that in a nephrectomized animal the liver may assume vicariously the function of hippuric acid synthesis. It does not prove that in the intact animal, even when the kidney is diseased, the same thing happens. Lackner, Levinson and Morse,<sup>14</sup> following Kingsbury's lead, studied the effect of liver injury on the hippuric acid synthesis in two dogs. The liver was injured by poisoning with hydrazine sulphate injected subcutaneously. This caused fatty degeneration of the liver but had no effect on the kidneys. A perusal of their data fails to convey clearly the idea of a marked participation of the liver in the hippuric acid synthesis. On the contrary, the extensive liver injury which they produced may be responsible for the failure in some preliminary steps in this process involving the formation of glycol, a step in which the liver doubtless plays a leading rôle. At any rate, the amino-acid elimination after the hydrazine injection does decrease, as is shown by their own studies. Furthermore, we do not know how much of the benzoic acid administered left the organism without being conjugated with glycol.

Lewis and Karr<sup>15</sup> have shown that hippuric acid synthesis is associated with a marked diminution in uric acid excretion. While the exact relationship between the two phenomena is not clearly understood, the

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13 Kingsbury, F. B., and Bell, E. T. The Synthesis of Hippuric Acid in Nephrectomized Dogs, *J. Biol. Chem.* **21** 297, 1915.

14 Lackner, E., Levinson, A., and Morse, W. The Rôle of the Liver in Hippuric Acid Synthesis, *Biochem. J.* **12** 184, 1918.

15 Lewis, H. B., and Karr, W. G. The Synthesis of Hippuric Acid in the Animal Organism. III. The Excretion of Uric Acid in Man After Ingestion of Sodium Benzoate, *J. Biol. Chem.* **25** 13, 1916.

observation is nevertheless very important as it indicates that corrolary phenomena in the liver and kidney occur during the synthesis

The recent extensive investigation of Delprat and Whipple,<sup>16</sup> who produced varying degrees of liver injury in dogs by the use of chloroform, bear out this point of view. These investigators found no change in the hippuric acid synthesis, except when the injury to the liver was very severe. On the other hand, Kingsbury and Bell's<sup>17</sup> investigation on rabbits which were made nephritic by injecting racemic tartaric acid revealed a considerable reduction in the per cent of synthesized hippuric acid besides the great increase in the free benzoic acid excretion following the injury.

Considering all the evidence, the conclusion cannot be escaped that the kidney is probably the place of hippuric acid synthesis. This does not exclude the possibility that under exceptional and wholly unnatural circumstances the liver, or some other organ, may not vicariously assume this function as well. Those, however, who are inclined more favorably to the hypothesis that the hippuric acid synthesis is normally a generalized function must still produce acceptable evidence for their view.

Kingsbury and Swanson,<sup>18</sup> in their recent study of the synthesis and elimination of hippuric acid, came to the conclusion that "in nephritis hippuric acid is synthesized completely, and as far as can be learned, at practically the same rate as in normal individuals." We have no criticism to offer of their experiments, except to point out that in our opinion their assumption that the free benzoic acid output is negligible is not entirely warranted. Inasmuch as they omitted the free benzoic acid from their determinations, this conclusion could more properly be interpreted as referring to the total benzoic excretion rather than to the hippuric acid synthesis. The results of our experiments with nephritic and cardiorenal patients, which we present in this paper, do not bear out their conclusion, as will be seen subsequently.

#### METHODS OF ANALYTICAL AND EXPERIMENTAL PROCEDURE

The hippuric acid output in the urine was determined according to the method recommended by Kingsbury and Swanson.<sup>19</sup> The hippuric acid of course, is formed through the conjugation of benzoic with

16 Delprat, G. D., and Whipple, G. H. Liver Function. Benzoate Administration and Hippuric Acid Synthesis, *J. Biol. Chem.* **49** 229, 1921.

17 Kingsbury, F. B., and Bell, E. T. The Synthesis of Hippuric Acid in Experimental Nephritis in the Rabbit, *J. Biol. Chem.* **20** 73, 1915.

18 Kingsbury, F. B., and Swanson, W. W. The Synthesis and Elimination of Hippuric Acid in Nephritis. A New Renal Function Test, *Arch. Int. Med.* **28** 220 (Aug.) 1921.

19 Kingsbury, F. B., and Swanson, W. W. A Rapid Method for the Determination of Hippuric Acid in Urine, *J. Biol. Chem.* **48** 13, 1921.

amino-acetic acid (glycocol), and the estimation of the hippuric acid depends on reactions involving, first, the breaking up of this combination and, second, measuring the amount of benzoic acid thus set free. The benzoic acid is then extracted with chloroform and titrated against a standard solution of sodium alcoholate. Inasmuch as benzoic acid which may already have been present in the urine, before the hydrolysis of hippuric, would likewise be extracted in the process, it is obvious that a correction must be made for the free benzoic acid or its salts appearing in the urine. Under some conditions the correction may be entirely negligible having no effect on the calculation of the amount of hippuric acid. Then, again, as in our experience at any rate, this correction may assume considerable importance. Therefore, in all our analyses we made separate determinations of the free benzoic acid even when we had reason to expect that this would be a negligible quantity. Our determinations were invariably on duplicate samples for both the total benzoic and the free benzoic acid in the urine.

The pathologic urines with which we worked all contained albumen in greater or smaller amounts, and it was necessary as a first step in the analysis to free the urines from this, as otherwise entirely erroneous results might have been obtained. For the purpose of deproteinizing, sodium hydroxid was added until the strongly acid urine reacted just faintly acid to litmus. Then 0.5 gm. tannic acid was added to every 100 c.c. of urine. A flocculent precipitate was formed in the presence of albumen which was filtered off after allowing the mixture to stand for a few minutes. Control experiments with normal urines of which one portion was treated in a similar manner with the tannic acid while the other was analyzed without such preliminary treatment, showed that this deproteinizing treatment had no effect on the results of the benzoic acid determination. The precipitate was filtered off and the filtrates were tested to ascertain that the deproteinization was complete.

Of the deproteinized urines 100 c.c. samples were immediately measured out into separatory funnels and saturated with ammonium sulphate. The mixture was then strongly acidified by the addition of 1 c.c. of concentrated nitric acid and extracted with four portions of washed freshly distilled chloroform (50, 35, 25 and 25 c.c., respectively). Raiziss and Dubin<sup>20</sup> recommend the use of toluol for this extraction, but Delprat and Whipple<sup>16</sup> have found that chloroform can be used with as good results. The formation of emulsions, which seems to be the chief reason for employing toluol instead of chloroform, did not cause us any trouble in the analyses, except in one instance, when the determination was lost on that account.

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<sup>20</sup> Raiziss, G. W., and Dubin, H. On the Estimation of Benzoic Acid in the Urine, *J. Biol. Chem.* **20** 125, 1915.

For determining the total benzoic acid, 50 c c portions of urine were usually taken unless much benzoic was expected, in which case 25 c c (diluted with water to 50 c c) was taken instead. The urine, mixed with 7.5 gm sodium hydroxid and 0.5 gm magnesium oxid was boiled down in a Kjeldahl flask to half this volume. One c c of saturated potassium permanganate was added and the contents of the flask well mixed by twirling. After cooling, the flasks were clamped in an upright position. A Hopkins condenser was inserted in the neck, through which a rapid stream of water has been kept flowing. Thirty c c of nitric acid was then poured cautiously into the flask and the contents digested for forty-five minutes over a gentle flame. The mixture became a clear, sparkling, yellow liquid which after cooling was transferred to a separatory funnel, saturated with ammonium sulphate and extracted with four portions of chloroform (50, 35, 25 and 25 c c, respectively), as in the case of the free benzoic acid determination. The combined chloroform extracts were now washed in a clean separatory funnel with Folin and Flander's acidulated sodium chlorid solution (saturated) and the chloroform drawn off through a filter into a clean Erlenmeyer flask. The combined and thoroughly washed extracts were now titrated with tenth normal sodium alcoholate, using phenolphthalein as an indicator.

The chloroform employed in our analyses was invariably purified before being used. For this purpose it was first washed with water and distilled, then washed again with saturated salt solution and redistilled. From time to time we checked up the quality of our chloroform by titrating an amount equivalent to that used for the extraction, but the addition of a single drop of the sodium alcoholate was sufficient to impart to the chloroform a deep red color.

The sodium alcoholate was prepared by weighing out the theoretic amount of metallic sodium and dissolving in absolute alcohol. This we prepared from purchased absolute alcohol, by boiling under a reflux condenser with calcium oxid and then redistilling it. The strength of the standard alcoholate was set by titrating measured quantities of an exact tenth normal benzoic acid prepared in toluol.

A word with regard to the procedure followed in the extraction with chloroform may not be amiss. The liquid to be extracted was shaken with the chloroform three times in succession, for periods of one minute, the two liquids being allowed to separate between successive shakings. We carried out determinations with known amounts of benzoic acid and satisfied ourselves that we recovered by this procedure the entire amount. To insure complete uniformity in the analyses the above routine was strictly adhered to in all determinations.

It is also, perhaps, well to mention that we made blank and check determinations to be sure that the analytic process as carried out by us was reliable in its results.

The patients on whom the hippuric synthesis test was performed were given a diet poor in benzoic acid, no fruit and only very little vegetables being allowed. They were also given no medication, not even alkali, during the entire period of the test. In later experiments, in order to limit the benzoic acid elimination as much as possible, a diet consisting exclusively of milk and toast was prescribed, starting at least one day before the test. In the earlier experiments we collected three twenty-four hour urines: one, as a preliminary urine, to find out the benzoic and hippuric acid output of the patient, the second urine (from twenty-four to forty-eight hours) followed the administration of a definite quantity either of sodium benzoate or benzoic acid, and a third urine (from forty-eight to seventy-two hours), to note the after-effect. The drug, either as benzoic acid or as the sodium salt, was administered exactly at the moment when the second urine sample was started. Inasmuch as the third urine proved of no particular importance in the test of the hippuric acid synthesis, it was omitted altogether in later experiments. Furthermore, to still further shorten the period covered by the test, a preliminary urine sample was taken for six hours (usually from 6 a. m. till noon). The patient received the substance at 12 noon, when the second urine sample was opened. It was closed at 6 p. m. giving a six hour urine following the benzoic acid ingestion. A third sample was then collected from 6 p. m. until noon the next day. The two last urines, therefore, gave the total benzoic and hippuric acid output for twenty-four hours after a known amount of benzoic acid was administered.

The urines were preserved with thymol and kept in a cool place. As soon as a sample was closed it was analyzed. To find out whether any hydrolysis of hippuric acid occurred spontaneously during the interval of time elapsing between the opening of the urine sample and the actual analysis, we examined aliquot portions of urine preserved in the usual manner immediately after being voided and at various times subsequently just as happened with our experimental urines. The same quantity of the urine was analyzed for free benzoic acid, and the same routine procedure was followed but we failed to find any change in the titration values within the limits of time occupied by our experiments. It is well to remember that the urines were always strongly acid. We are satisfied, therefore, that the changes in free benzoic acid elimination which we observed under the circumstances of our tests were not due to the setting free of benzoic acid from its combination with glycolic (i. e., the decomposition of hippuric acid) but must be regarded as being actually excreted by the kidneys.

## DISCUSSION OF CASES

Before discussing the hippuric acid synthesis and the excretion of benzoic acid in a number of hospital patients, it is well to detail our findings with normal persons. We shall, therefore, report a few tests performed on perfectly healthy subjects.

In the accompanying graphs free benzoic acid is represented by the unshaded portion. The cross striated blocks represent the total benzoic acid while the longitudinally striated ones represent the hippuric acid. The arrows point to the theoretical level of hippuric and benzoic acid excretions.

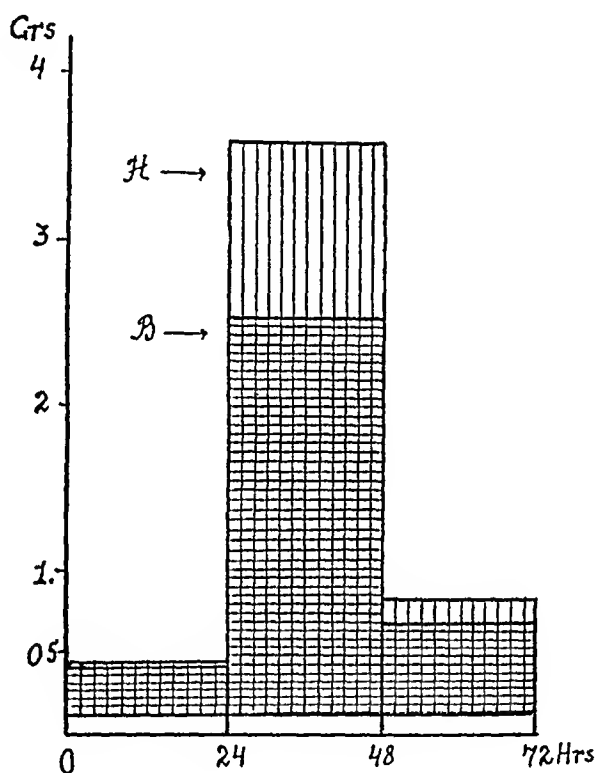


Fig 1—Case 1

CASE 1—H M J A twenty-four hour urine sample was collected before the subject took 24 gm sodium benzoate dissolved in water. This preliminary urine contained 0.409 gm of total benzoic acid. Inasmuch as 0.117 gm was in free condition, the remaining benzoic acid was bound to form 0.428 gm hippuric acid. The twenty-four hour urine following the ingestion of 24 gm sodium benzoate ( $\approx 2.033$  gm benzoic acid) contained 2.556 gm benzoic acid. The free benzoic acid was practically unchanged (0.122 gm) and the hippuric acid output was 3.572 gm. When the correction for the hippuric and benzoic acid content of the daily urine is made, the subject eliminated 5 per cent more than the theoretically expected amount of both. During the third twenty-four hour period the urine contained 0.667 gm benzoic acid. The benzoic acid in free condition was still practically the same as on the previous two days (0.111 gm), and the hippuric acid output was 0.815 gm.

CASE 2—S M The preliminary twenty-four hour urine of this subject contained 1.036 gm benzoic acid and of this amount 0.173 gm was not conjugated, the hippuric acid output being thus 1.267 gm. The subject took 24 gm sodium benzoate in water and in the next twenty-four hours the benzoic acid



content of the urine reached 3202 gm. The free benzoic acid increased to 0307 gm, the remainder being conjugated in the form of 4248 gm hippuric acid. The urine collected for the third twenty-four hour period contained 1172 gm benzoic acid. The free benzoic acid elimination diminished again to 0261 gm leaving the remainder conjugated in 1336 gm of hippuric acid. Making the proper corrections, the subject synthesized 100 per cent of the theoretically expected amount of hippuric acid. The benzoic acid excretion during this twenty-four hour period following the benzoic administration was actually 4 per cent over and above the theoretic amount, the excess being in the form of free benzoic acid.

In either case with the normal subject, the benzoate ingestion not only resulted in a complete synthesis of benzoic to hippuric acid but

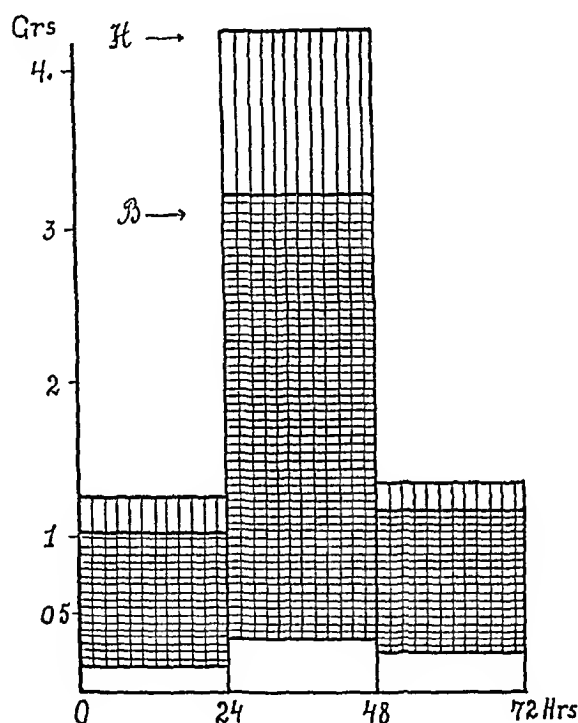


Fig 2—Case 2

the kidney was apparently stimulated to greater activity. This stimulation of the kidney is seen not only in the excess over the theoretic amount which was recovered from the urines passed within twenty-four hours after the benzoate administration but also in an increased hippuric acid output forty-eight hours later. This last fact gains significance by contrast with what is usually found under pathologic conditions, as will be pointed out subsequently.

**CASE 3—S M** Tests were also made in which benzoic acid was given in place of the sodium benzoate. The results are not essentially different from those presented in the above experiments but we shall report one example. The subject was on a diet poor in benzoic acid (fruit and vegetable free). The preliminary urine for six hours contained 0299 gm benzoic acid and 0425 gm hippuric, the free benzoic acid being practically negligible (0009 gm). Two

grams benzoic acid was then taken in gelatin capsules and the urine analyzed every three hours during the day. In the first three hours 82 per cent of the theoretic amount of hippuric acid appeared in the urine. By the end of six hours virtually 98 per cent of the benzoic acid was already eliminated and 96 per cent of the expected synthesis in the hippuric acid occurred.

This corresponds to Lewis' findings where, with much larger doses (from 6 to 10 gm) of sodium benzoate, about 90 per cent was recovered in the form of hippuric acid in the five or six hour urine.<sup>21</sup> In the eighteen hours completing the twenty-four hours' sample, little further change took place, but the total benzoic acid recovered within the twenty-four hours was 99 per cent of the theoretical.

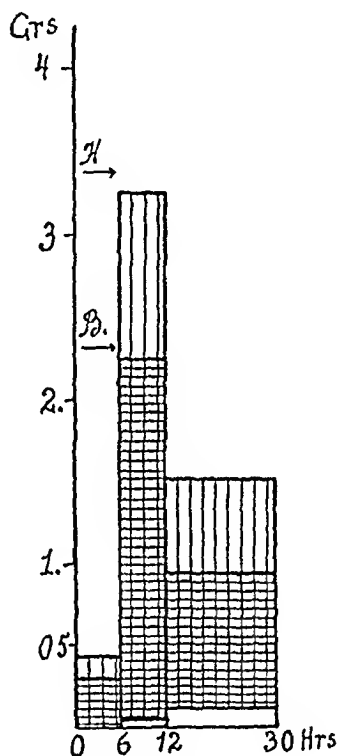


Fig 3—Case 3

We will now consider the hippuric acid synthesis and benzoic acid excretion in a number of pathologic cases.

CASE 4—L. E. P., female, aged 37, came to one of us (G. P. P.) for advice Sept 30, 1921.

*History*—Six weeks ago she first noticed some puffiness about the eyes and hands. In the morning the swelling became more marked. Her legs are now swollen. She feels tired and has an occasional headache. She passes a small amount of urine. No nocturia is present.

*Past Illness*—Influenza in 1918, when she remained in bed four weeks. She was in a hospital two weeks in 1919 for "stomach trouble." In May, 1921, she had tonsillitis with a complicating peritonsillar abscess. Measles, pertussis, and diphtheria during childhood.

<sup>21</sup> Lewis, H. B. The Synthesis and Rate of Elimination of Hippuric Acid After Benzoate Ingestion in Man, *J Biol Chem* **18** 225, 1914.

*Physical Examination*—Temperature, 98.6 F, pulse, 70, respiration, 20. The legs are edematous and there is puffiness about the eyes in the morning. Eye-grounds negative, pupils equal and active, tonsils hypertrophied, many filled teeth, roentgenogram of teeth revealed fourteen peri-apical abscesses. The lungs are quite normal. The heart sounds are normal. The heart is normal in size and the rhythm is regular. The blood vessels are not thickened. Blood pressure, 135/80. The abdomen is negative. The reflexes are normal.

*Laboratory Examination*—Blood Wassermann test negative. Red blood cells, 4,210,000, white blood cells, 6,900, hemoglobin, 80 per cent. 100 cc of blood contained 91 mg sugar, 48 mg nonprotein nitrogen and 18 mg uric acid.

Urine Acid, cloudy, specific gravity, 1.024, albumin, four plus, no sugar. Microscopic examination granular and hyaline casts, white blood cells and an occasional red blood cell.

*Diagnosis*—Subacute diffuse nephritis.

Tests of Kidney Function Phenolsulphonephthalein output in two hours and ten minutes, 45 per cent.

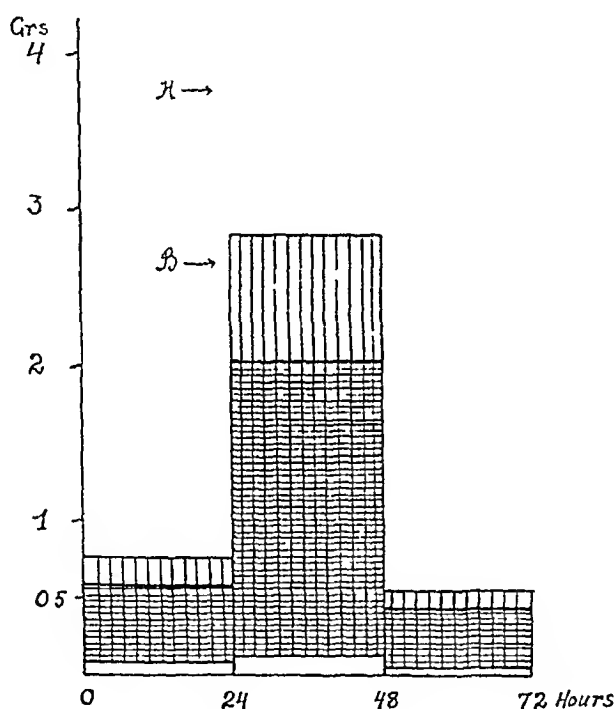


Fig 4—Case 4

*Hippuric Acid Test* The preliminary twenty-four hour urine contained 0.604 gm benzoic acid of which 0.080 gm was free and the remainder conjugated in the form of 0.758 gm hippuric acid. The patient received 24 gm sodium benzoate and following the administration another twenty-four hour urine was collected. This urine contained 2.022 gm benzoic acid of which 0.120 gm was free. The remaining portion was conjugated to form 2.822 gm hippuric acid. Since the theoretically expected amount of total benzoic acid was 2.634 gm only 77 per cent was recovered. Of the expected 3.736 gm hippuric acid only 76 per cent was synthesized in twenty-four hours. A third twenty-four hour sample contained 0.428 gm total benzoic acid with 0.054 gm in the free state. It contained, therefore 0.548 gm hippuric acid.

CASE 5—S. S., female, aged 36, admitted to the University Hospital Feb 9, 1922.

*History*—She noticed about a year ago that it was hard to see with the left eye. The dimness of vision increased until two weeks ago a similar process attacked her right eye. She suffers shortness of breath on exertion. The urine is abundant with nocturia two or three times.

*Past Illness*—For several months in 1906 she suffered from swollen ankles. This was usually worse in the evening. She had measles and diphtheria during childhood.

*Physical Examination*—Temperature, 99 F, pulse, 80, respiration, 20. Patient is rather heavy with slight edema of the ankles. She has "albuminuric retinitis" in both eyes, more marked on the left side, pupils equal and active, tonsils congested and hypertrophied, pyorrhea, pus can be expressed from lower incisors and there are four teeth with large cavities. The lungs are quite normal, the heart is moderately enlarged and the aortic second is accentuated. The blood vessels are somewhat thickened. Blood pressure, 220/170. The liver can be felt one finger breadth below the costal margin. The reflexes are normal.

*Laboratory Examination*—Blood. Wassermann test negative. Red blood cells, 4,147,000; white blood cells, 8,400; hemoglobin, 85 per cent. 100 cc of blood contained 120 mg sugar, 65 mg nonprotein nitrogen, and 4.5 mg uric acid.

Urine. Acid, specific gravity, 1.010, albumin, three plus, no sugar. Microscopic examination: hyaline casts.

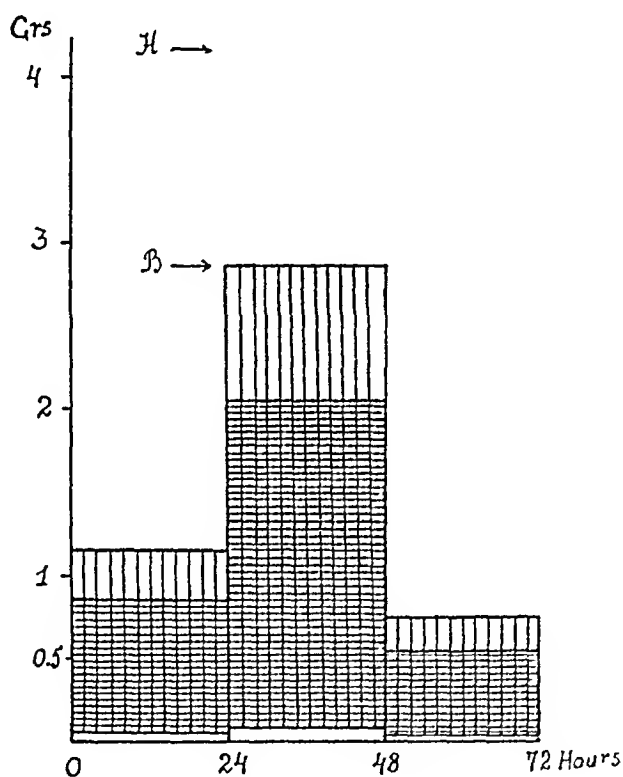


Fig 5—Case 5

*Diagnosis*—Cardiovascular renal disease.

*Tests of Kidney Function*—Phenolsulphonephthalein output in two hours ten minutes, 15 per cent.

*Hippuric Acid Test*—The preliminary urine sample for twenty-four hours contained a total of 0.848 gm benzoic acid of which 0.058 gm were in free condition, the hippuric acid content was, therefore, 1.159 gm. The patient received 24 gm sodium benzoate and a twenty-four hour urine following the ingestion contained a total of 2.046 gm benzoic acid with 0.082 gm of the free acid, the remaining fraction conjugated to form 2.881 gm hippuric acid. Comparing these quantities with those theoretically expected, only 59 per cent of the total benzoic and 58 per cent of the hippuric acid were recovered in the twenty-four hours. During the third twenty-four hour period the patient eliminated a total of 0.545 gm benzoic acid. The free benzoic acid had diminished to 0.038 gm, the rest being conjugated to form 0.744 gm of hippuric acid.

CASE 6—F K K, male, aged 53, admitted to the University Hospital Feb 22, 1922

*History*—Patient returns to hospital on account of edema affecting the lower extremities, which is worse in the evening. Dyspnea and precordial pain. He was admitted to the hospital June 9, 1921, for six weeks and again Sept 6 1921, for three months, both times for cardiac decompensation.

*Past Illness*—At 18 he had acute articular rheumatism, denies having had any other diseases.

*Physical Examination*—The patient is poorly nourished and not well developed. Eyegrounds: small retinal hemorrhages in both eyes, pupils equal and active, tonsils small, teeth in good condition. The lungs show evidence of congestion at both bases. The heart is markedly enlarged, the rhythm is irregular and there is a systolic murmur at the apex. The blood vessels are sclerotic. Blood pressure, 205/125. The liver is enlarged two fingers breadth below the costal margin. There is edema about the ankles extending to the knees.

*Laboratory Examination*—Blood: Wassermann test, negative. Red blood cells, 4,000,000, white blood cells, 7,200, hemoglobin, 80 per cent, 100 c.c. blood contained 100 mg. sugar, 61 mg. nonprotein nitrogen and 45 mg. uric acid.

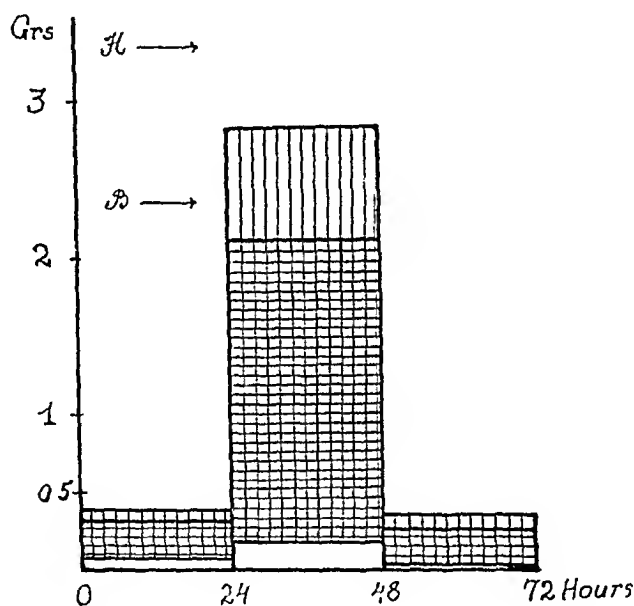


Fig 6—Case 6, first test

Urine: Acid, specific gravity, 1.015, albumin, one plus, no sugar. Microscopic examination: hyaline and granular casts.

*Diagnosis*—Cardiovascular renal disease.

Tests of Kidney Function: Phenolsulphonephthalein output in two hours ten minutes, 40 per cent.

*Hippuric Acid Test* This has been repeated three times for this patient. First test, March 15 to 18. The preliminary twenty-four hour urine contained 0.322 gm benzoic acid, of which 0.059 gm was free. The hippuric acid was, therefore, 0.387 gm. The patient was given 24 gm sodium benzoate, and a second twenty-four hour urine was collected. This contained 2.115 gm benzoic acid with 0.176 gm as free benzoic. The hippuric acid was thus 2.845 gm. Only 88 per cent of the theoretically expected total benzoic acid and 83 per cent of the hippuric acid was recovered. In the next twenty-four hours the urine contained 0.273 gm of total benzoic acid, and as there was present 0.027 gm of the free acid, 0.362 gm were eliminated in the form of hippuric acid.

Second test, March 21-23 The test was performed as before, except that 2 gm benzoic acid put up in gelatin capsules was administered instead of sodium benzoate. The preliminary twenty-four hour urine is very similar to that of the first test. It contained 0.287 gm benzoic acid with 0.031 gm in the free state and the rest conjugated to form 0.376 gm hippuric acid. In the twenty-four hours following the ingestion of the benzoic acid 1.830 gm of total benzoic acid was excreted. Of this 0.332 gm was free acid and the rest was conjugated in 2.197 gm hippuric acid. This time we recovered, therefore, only 77 per cent of the benzoic acid and 62 per cent of the theoretically expected hippuric acid. During the third twenty-four hour period the total benzoic acid in the urine was 0.381 gm and the free benzoic acid returned to the level of the preliminary urine (0.052 gm). The hippuric acid was 0.483 gm.

Third Test About a month later we applied the test once more in a somewhat modified form. The patient's diet was limited to milk and toast. Unfortunately, the patient was unwilling to cooperate and could not be persuaded

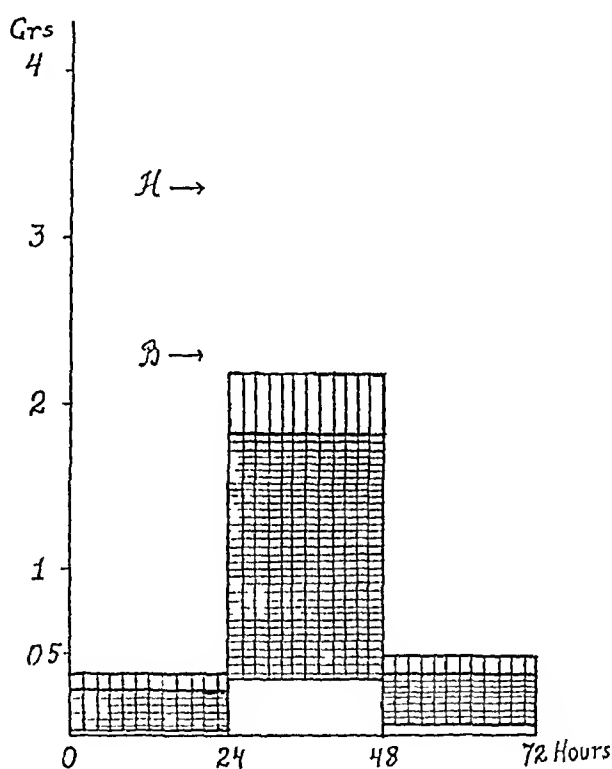


Fig 7—Case 6, second test

to take enough liquid, either milk or water. In consequence, his urinary output diminished very considerably. Although we do not attach much significance to this test, we are recording it because of the general interest it has with regard to the question of hippuric acid synthesis.

After the patient had been on milk and toast for one day, a six hour urine sample was collected and 2 gm benzoic acid in capsules was given to the patient. There was only 40 cc of the preliminary urine and this contained 0.051 gm benzoic acid or 0.076 gm hippuric acid. A second six hour urine sample was obtained after the patient had taken 2 gm benzoic acid. This second sample (65 cc) contained 0.357 gm of total benzoic acid. As there was 0.059 gm of free acid, he eliminated 0.478 gm hippuric acid. We find, therefore, that in six hours the patient excreted only 15 and 14 per cent, respectively, of the theoretically expected benzoic and hippuric acid. A third urine (315 cc) was collected for eighteen hours (completing the twenty-four hour sample following the benzoic acid ingestion) and this contained 0.939 gm benzoic acid. Since

0.067 gm was free benzoic the rest made up 1.280 gm hippuric acid. The total elimination for the twenty-four hour period was, therefore, 55 per cent of the benzoic acid administered and 50 per cent of the expected hippuric synthesis.

The much reduced output of both hippuric and benzoic acid noted in this last test we ascribe to the fact that the patient's urinary secretion during this period was very scanty. In fact, when the results of the three tests performed for this patient are compared, it is obvious that the hippuric acid synthesis follows closely the total urinary excretion. It would be difficult to understand these coincident changes in kidney activity if the hippuric acid synthesis was not a kidney function. The third test also emphasizes the necessity of providing an ample amount of fluid in order that the urine output should be sufficient and the

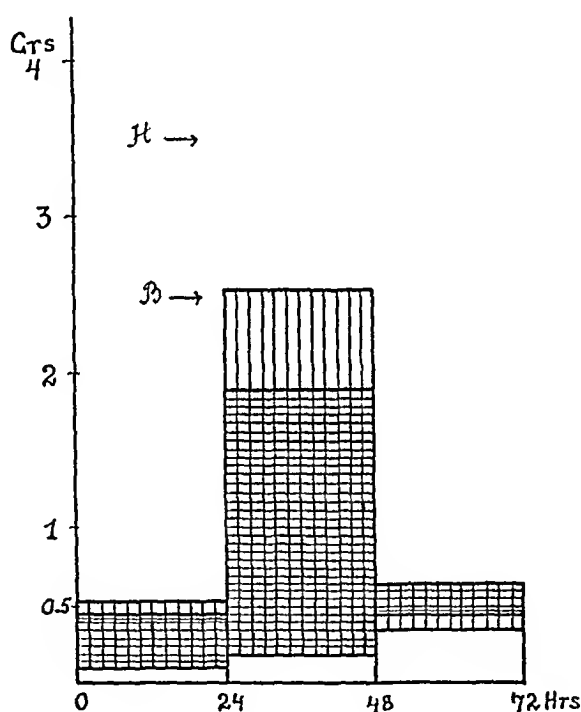


Fig 8—Case 7, first test

hippuric acid synthesis should not be interfered with on that account. It must further be pointed out that in patients whose urine output is naturally limited the test may lead to erroneous conclusions.

**CASE 7**—H. R., male, aged 20, admitted to University Hospital, Jan 19, 1922.

**History**—One month ago patient developed a general anasarca. The swelling especially in the mornings, was most marked in the legs and face. Complaints of shortness of breath. There is nocturia from three to four times.

**Past Illness**—The patient was in the hospital two and one-half years ago for acute nephritis following tonsillitis. He remained in the hospital for a while and has been up and about since, working most of the time, until the present illness. He has had mumps, measles and frequent attacks of tonsillitis.

**Physical Examination**—Patient presents the characteristic pasty appearance. Eyegrounds negative, pupils equal and active, tonsils have been removed, pil-

lars are congested, teeth are in good condition The lungs are negative The heart is slightly enlarged, with an accentuated second aortic sound Blood pressure, 180/110 The abdomen is negative The reflexes are sluggish Edema about the ankles

*Laboratory Examination* — Blood Wassermann test negative Red blood cells, 3,136,000, white blood cells, 14,400, hemoglobin, 60 per cent, 100 cc of blood contained 98 mg sugar, 117 mg nonprotein nitrogen, and 65 mg uric acid

Urine Alkaline, specific gravity, 1.013, albumin four plus, no sugar

Microscopic Examination Numerous granular casts, red cells

*Diagnosis* — Chronic diffused nephritis

Tests of Kidney Function Phenolsulphonephthalein output in two hours and ten minutes, 10 per cent

Hippuric Acid Test The preliminary twenty-four hour urine contained 0.448 gm of total benzoic acid As there was 0.089 gm of free benzoic acid the remainder was bound in 0.527 gm hippuric acid Following the intake of 2, 4 gm sodium benzoate, the twenty-four hour urine contained 1.879 gm benzoic acid with 0.165 gm in the form of acid The hippuric acid output was, therefore, 2.515 gm Introducing the necessary corrections,

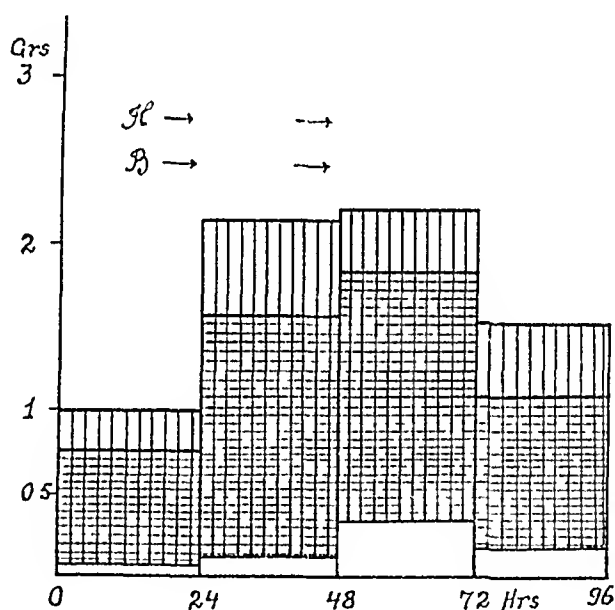


Fig 9—Case 7, second test

we find that in the twenty-four hours 76 per cent of the benzoic acid and 72 per cent of the theoretically expected hippuric acid was recovered In the next period of twenty-four hours the patient eliminated 0.634 gm benzoic acid The free benzoic acid in the urine showed a further increase to 0.333 gm The hippuric acid output during the third twenty-four hour period was, therefore, 0.441 gm At a later time we repeated the test, administering 12 gm sodium benzoate on two consecutive days instead of the single dose of 24 gm The results of this test (Fig 9) are essentially the same as that of the previous test

CASE 8—C W, male, aged 72, was admitted to University Hospital March 21, 1922

*History* — Patient has had precordial pain and shortness of breath at intervals for several years In the past five months dizziness has become troublesome There has been nocturia for three years

22 During the hippuric acid tests alkalinization of the patient was discontinued and the urines were invariably strongly acid



*Past Illness*—Pneumonia in adult life

*Physical Examination*—Patient is well nourished Eyegrounds are negative, pupils equal and active, tonsils negative, teeth all extracted Lungs show evidences of slight congestion at the bases The heart is slightly enlarged, sounds distinct, no murmurs Blood pressure, 170/85 Abdomen is negative Extremities normal

*Laboratory Examination*—Blood Wassermann test negative Red blood cells, 5,280,000, white blood cells, 6,600, hemoglobin, 75 per cent, 100 cc blood contained 110 mg sugar, 48 mg nonprotein nitrogen

Urine Acid, specific gravity, 1.020, albumin, one plus, no sugar Microscopic examination hyaline casts

*Diagnosis*—Cardiovascular renal disease

Tests of Kidney Function Phenolsulphonethalein output in two hours and ten minutes, 50 per cent

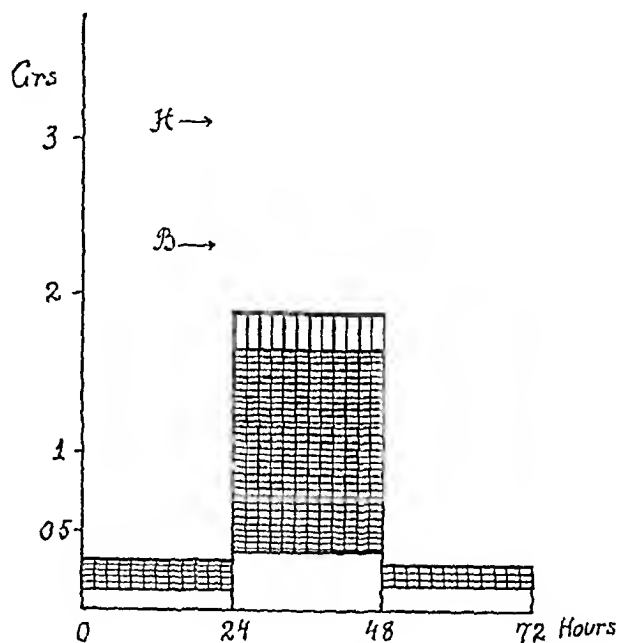


FIG 10—Case 8, first test

*Hippuric Acid Test* The test has been repeated several times with this patient *First Test* The preliminary twenty-four hour urine sample contained 0.311 gm benzoic acid, with 0.098 gm in a free state The remainder formed 0.313 gm of hippuric acid Following the ingestion of 24 gm of sodium benzoate, the twenty-four hour urine contained 1.665 gm benzoic with 0.375 gm as free acid The hippuric acid output corresponding to the remainder of the benzoic acid was 1.892 gm When the proper correction for the normal elimination is made, 67 per cent of the ingested benzoic acid was recovered in the twenty-four hours and 53 per cent of the theoretic amount of hippuric acid The third twenty-four hour urine is much lower in benzoic acid content than the preliminary—only 0.290 gm of total benzoic acid being present The hippuric acid excretion was 0.200 gm

*Second Test* This test was applied five days later, the only modification being that 2 gm benzoic acid in gelatin capsules was administered this time The preliminary twenty-four hour urine contained 0.544 gm of total benzoic acid The free benzoic acid in the urine was still high, 0.171 gm, so that 0.547 gm of hippuric acid was eliminated in the twenty-four hours Following the ingestion of the 2 gm of the benzoic acid, the twenty-four hour urine

contained 2.272 gm benzoic acid. As was also the case in the first test, the free benzoic acid increased to 0.325 gm. The patient excreted, therefore, 2.857 gm hippuric acid. Making the necessary corrections, we find that this time we recovered 87 per cent of the benzoic acid and 79 per cent of the hippuric acid theoretically expected. In the subsequent twenty-four hours there was only 0.420 gm total benzoic acid. The free benzoic acid determination was lost and the hippuric acid output could not, therefore, be calculated accurately, but it is evident that it was appreciably lower than in the preliminary twenty-four hours.

**Third Test** In view of the fact that this patient showed persistently a relatively high free benzoic acid excretion, we put him exclusively on a milk and toast diet. A six hour preliminary urine sample was obtained in which the free benzoic acid was reduced to a practically negligible level. The total

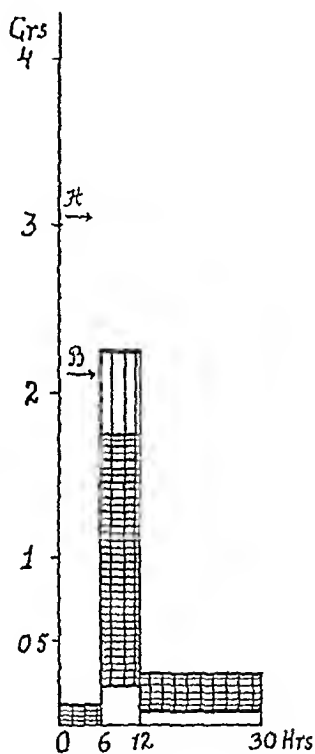


Fig 11—Case 8, third test

benzoic acid for these six hours was 0.088 gm and the hippuric acid was 0.116 gm. The patient was given 2 gm benzoic acid in capsules. The urine for the next six hours contained 1.757 gm total benzoic acid and the free benzoic acid increased to 0.224 gm. The hippuric acid output was 2.248 gm. In six hours following the ingestion of benzoic acid, 84 per cent was recovered in the urine, of which 73 per cent was in the form of hippuric acid. The urine for the next eighteen hours contained 0.281 gm benzoic acid (with 0.085 gm in the free state) and 0.288 gm hippuric acid. When the total elimination for twenty-four hours following the benzoic acid administration is considered, we find that during the entire period 84 per cent of benzoic and 71 per cent of hippuric acid have been recovered. In other words, there has been practically no change from what had happened in the first six hours.

**CASE 9**—A W, male, aged 32, was admitted to the University Hospital March 6, 1922.

**History**—Three years ago patient was refused life insurance on account of kidney trouble, albumin in the urine, and high blood pressure.

**Past Illness**—Measles and chickenpox during childhood and influenza in 1918.

*Physical Examination*—Patient is well nourished and well developed. Eye-grounds are negative, pupils equal and accurate, tonsils buried, teeth are in good condition. Lungs are negative. The heart very slightly enlarged. Blood pressure, 175/110. Abdomen negative. Reflexes active.

*Laboratory Examination*—Blood Wassermann negative. Red blood cells, 3,900,000, white blood cells, 6,200, hemoglobin, 74 per cent, 100 c c contained 98 mg sugar, 74 mg nonprotein nitrogen, 54 mg uric acid<sup>23</sup>.

Urine Acid, specific gravity, 1.013, albumin, two plus, no sugar. Microscopic examination hyaline and granular casts.

*Diagnosis*—Chronic diffuse nephritis.

Tests of Kidney Function Phenolsulphonephthalein output in two hours and ten minutes 15 per cent.

Hippuric Acid Test A preliminary twenty-four hour urine was collected to determine the base line for the benzoic and hippuric acid excretion. The total benzoic acid output was found to be 0.471 gm. Since the free benzoic acid

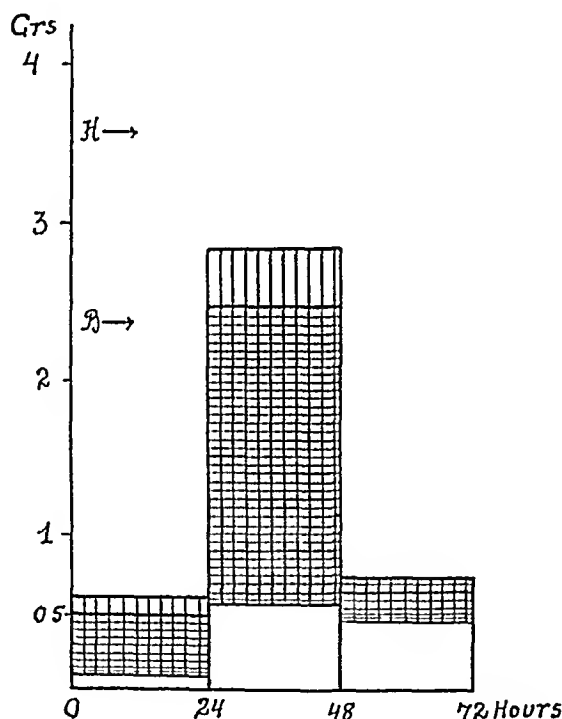


Fig 12—Case 9

was 0.081 gm there was 0.572 gm of hippuric acid. The patient received 24 gm sodium benzoate and a twenty-four hour urine was again collected. The total benzoic acid output rose to 2.428 gm and of this amount 0.534 gm was in the form of free benzoic acid. The hippuric acid output was, therefore, 2.778 gm. Correcting for the normal excretion, 96 per cent of the ingested benzoic acid was recovered in twenty-four hours. Owing to the fact that a large amount of the benzoic acid was unconjugated, only 74 per cent of the theoretically expected hippuric acid was synthesized and excreted. The third twenty-four hour urine presented considerable interest. The total benzoic acid output was relatively high (0.719 gm) and the free benzoic acid still remained at a very high level (0.467 gm) so that only 0.459 gm of hippuric acid were eliminated.

23 A blood analysis made two and a half months later gave the following results: 150 mg sugar, 90 mg nonprotein nitrogen, 31 mg uric acid, and 36 mg creatinin.

When the benzoic and hippuric acid output for the three consecutive days occupied by the test are summed up, we note that 3.618 gm benzoic acid were recovered. Making the necessary corrections on the basis of the data for the preliminary period and also for the amount administered in the form of 2.4 gm sodium benzoate, we find a small excess of benzoic acid (0.175 gm above the theoretically expected amount). When we calculate in a similar manner the hippuric acid, we find that only 83 per cent of the expected synthesis has taken place. These results are significant, especially as we are dealing in this case with a true nephrosis. The kidney of the nephritic patient is evidently quite capable of excreting benzoic acid and the full amount that could be expected passed through the urine. The matter is entirely different when we consider the kidney's synthetic ability, and even forty-

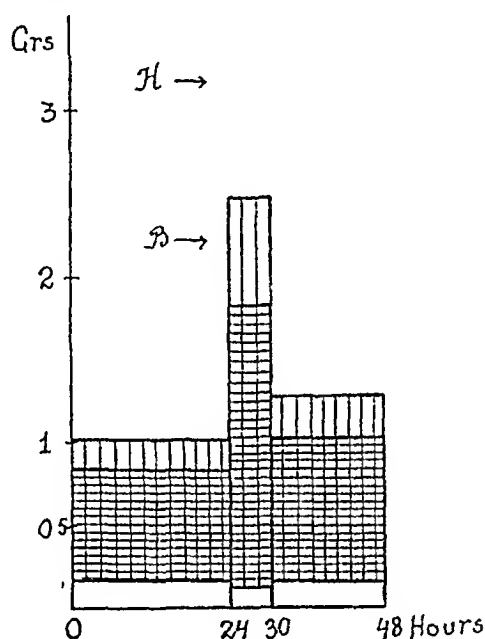


Fig 13—Case 10, first test

eight hours after the administration of sodium benzoate only 83 per cent of the possible synthesis was accomplished. It is evident, therefore, that the excretion of benzoic acid by the kidney and its synthesis to hippuric acid are either distinct functions or are carried out by different structural parts of the kidney. We shall see other instances in which, unlike the ones discussed previously, a high degree of excretory power goes hand in hand with a relatively low grade of synthetic power. If the synthesis of hippuric acid occurred anywhere else in the body outside the kidney, these results would be difficult to interpret, as there is no evidence of a lesion anywhere except in the kidney.

CASE 10—J. F. L., male, aged 62, was admitted to the University Hospital April 12, 1922.

*History*—For more than ten years the patient has suffered shortness of breath on exertion, frequency of urination, with nocturia. At times he has

had severe asthmatic attacks Three weeks before admission he was seen by us and at that time there was a general anasarca, especially marked in the abdominal vaults and scrotum

*Past Illness* — Measles, mumps and pertussis during childhood He had malaria in 1885 and again in 1908

*Physical Examination* — Patient is fairly well developed and well nourished Eyegrounds are negative, pupils equal and active, tonsils normal, teeth in poor condition Emphysematous type of chest, hyperresonant throughout, dry râles at the end of expiration Heart moderately enlarged, systolic murmur at the apex, aortic second accentuated The arteries are somewhat thickened Blood pressure, 150/80 Abdomen negative Reflexes active

*Laboratory Examination* — Blood Wassermann test negative Red blood cells, 2,230,000, white blood cells, 7,000, hemoglobin, 50 per cent, 100 c c of blood contained 109 mg sugar, 56 mg nonprotein nitrogen and 48 mg uric acid

Urine Acid, specific gravity, 1.010, albumin, two plus, no sugar Microscopic examination hyaline and granular casts, many white blood cells and a few red blood cells

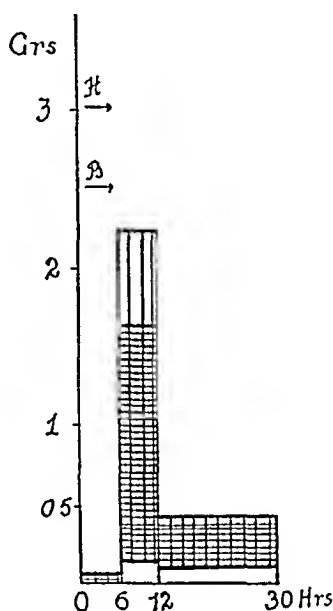


Fig 14—Case 10, second test

*Diagnosis*—Cardiovascular renal disease

Tests of Kidney Function Phenolsulphonephthalein output in two hours ten minutes, 35 per cent

*Hippuric Acid Test* First test A preliminary twenty-four hour urine was collected It contained 0.837 gm total benzoic acid, with 0.142 gm in the free state The hippuric acid was therefore 1.019 gm The patient ingested 2 gm benzoic acid put up in gelatin capsules, and a six hour urine sample was taken immediately afterward This contained 1.819 gm of total benzoic acid The free benzoic acid elimination rose to 0.124 gm in six hours The hippuric acid output in the same time was 2.488 gm with proper corrections, therefore, 81 per cent of the ingested benzoic acid was recovered in six hours, and 76 per cent of the theoretically expected hippuric acid synthesis A third urine for eighteen hours contained 1.015 gm of total benzoic acid, of which 0.143 gm was in an unconjugated state The hippuric acid output was 1.280 gm For the entire twenty-four hour period following the administration of 2 gm of benzoic acid, 100 per cent of the complete dose was recovered in the urine and 95 per cent of the expected hippuric acid The results of this test are, therefore, comparable to those found in Case 10

**Second Test** Owing to the fact that the free benzoic acid elimination of this patient tended to be rather high on the usual diet, which we gave during the test, we repeated the test with the patient on a milk and toast diet. Even then he still eliminated about 120 mg of free benzoic acid in twenty-four hours. Only after he had been on this diet for five days, did the urine become practically free from unconjugated benzoic acid. A preliminary urine sample for six hours contained 0.050 gm of total benzoic acid and the hippuric acid output was 0.065 gm. The patient was given 2 gm of benzoic acid in capsules and a second urine sample for six hours was collected.

This time the urine contained 1.648 gm total benzoic acid. The free benzoic acid rose markedly from 0.006 gm to 0.130 gm in the six hours. The hippuric acid output was 2.228 gm. Introducing the proper corrections, we find that 80 per cent of the ingested benzoic acid was eliminated in six hours, while 74 per cent of the theoretical amount of hippuric acid was synthesized. A third urine was collected for the next eighteen hours, thus completing the twenty-four hour sample. This last urine contained 0.371 gm total benzoic acid. The free

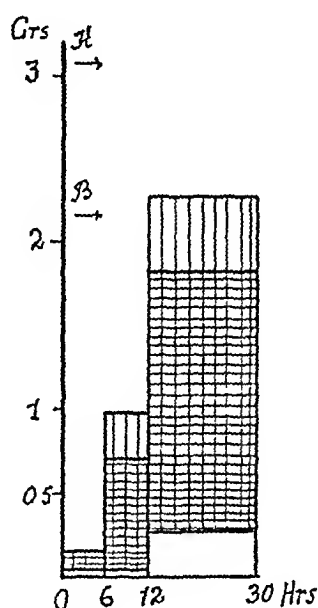


Fig 15—Case 11, first test

benzoic acid diminished greatly and was only 0.087 gm. The hippuric acid output was 0.417 gm. The total elimination for twenty-four hours included, therefore, 91 per cent of the ingested benzoic acid, and 81 per cent of the expected hippuric acid synthesis had taken place. It should be noted that about three weeks had elapsed between these two tests and that the patient had developed in the meantime signs of cardiac decompensation.

**CASE 11**—J. L. P., male, aged 42, was admitted to the University Hospital April 20, 1922.

**History**—Six months ago patient first noticed that he was becoming weak. He has suffered frequent attacks of dizziness, more marked the last six weeks. There has been an increasing amount of urine, and the nocturia has increased in the last four months from one to five or six times. There has been some puffiness about the eyes, but no swelling.

**Past Illness**—During childhood whooping cough, chickenpox and measles. Five years ago he had malaria. He gives a history of a chancre in 1907.

**Physical Examination**—A well formed and well nourished young man, somewhat pale and with some edema about the eyes. Eyegrounds negative, pupils equal and active, tonsils normal, teeth in poor condition. Cervical glands

barely palpable Lungs are negative Heart enlarged, both second sounds markedly accentuated Blood pressure, 230/140 Abdomen negative Extremities and reflexes normal

*Laboratory Examination*—Blood Wassermann test, three plus positive Red blood cells, 4,350,000, white blood cells, 7,500, hemoglobin, 75 per cent, 100 c c blood contained 132 mg sugar, 89 mg nonprotein nitrogen, 83 mg uric acid

*Diagnosis*—Chronic diffuse nephritis

Tests of Kidney Function Phenolsulphonephthalein output in two hours and ten minutes, 9 per cent

Hippuric Acid Test First test This was made soon after patient was admitted to the hospital For two days previous to the test he was on a milk and toast diet A six hour preliminary urine sample contained 0.146 gm of total benzoic acid Unfortunately, the free benzoic acid determination was not successful, but it was approximately 0.046 gm There was, therefore, 0.148 gm hippuric acid The patient took 2 gm benzoic acid in capsules In the next six hours his urine showed 0.702 gm of benzoic acid (0.037 gm unconjugated)

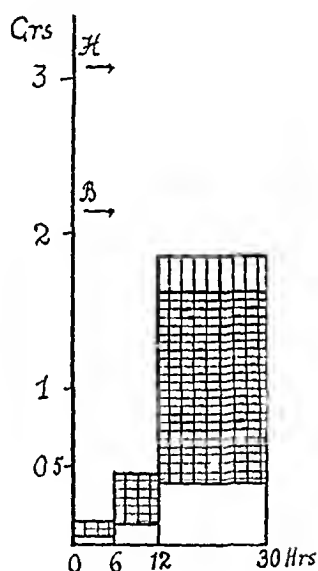


Fig 16—Case 11 second test

and 0.976 gm of hippuric acid He, therefore, excreted 33 per cent of the administered benzoic acid and synthesized 28 per cent of the theoretical amount of hippuric acid In the next eighteen hours, however, his urine contained 1.815 gm of benzoic acid The amount of unconjugated acid increased to 0.259 gm The hippuric acid output was 2.282 gm In twenty-four hours following the benzoic acid ingestion—making proper allowance for the normal elimination—the patient excreted 100 per cent, or the full dose of the benzoic acid, and 91 per cent of the possible synthesis into hippuric acid occurred in that time The results with this patient are essentially the same as obtained in the previous two cases, except that the rate of excretion was much slower

Soon after the first test the patient's condition began to grow worse He developed albuminuric retinitis, severe headaches, etc A second test was made on him ten days later, four days before he died of uremic coma

Second Test The preliminary six hour urine contained 0.153 gm benzoic acid with 0.050 gm as the unconjugated acid The hippuric acid output was, therefore, 0.152 gm It is interesting to observe that in spite of the fact that the patient had been limited to a diet as nearly as possible poor in benzoic acid, he continued to excrete relatively large amounts of free benzoic acid and we never succeeded in his case to lower the free benzoic acid excretion to the

point where it would be entirely negligible for the hippuric acid calculation. After administering 2 gm of benzoic acid in gelatin capsules a second six hour urine was collected, which contained only 0.615 gm total benzoic acid. The free benzoic acid increased to 0.192 gm, i. e., almost fourfold over that of the preliminary period, and the hippuric acid output was 0.620 gm. In this test only 23 per cent of the total benzoic acid ingested and 16 per cent of the possible hippuric acid were recovered in six hours, a considerable reduction since the previous test. The third urine for the next eighteen hours contained 1.620 gm total benzoic acid with a large amount (0.361 gm) in the unconjugated state, so that only 1.847 gm hippuric acid was excreted. It is to be noted and will be seen clearly from the charts, that the course of the benzoic and hippuric acid excretion is similar in both tests, except that in the second test, made three days before the onset of uremia, which led to coma, and soon terminated in death, only 81 per cent of the administered benzoic acid was recovered in the twenty-four hour urine, while of the theoretic amount of hippuric acid only 63 per cent was actually synthesized.

With the onset of the comatose condition, the composition of the blood showed unmistakable evidence of its uremic nature. Two samples of blood obtained thirty hours before death and soon after death occurred (taken directly from the heart) had the following composition:

100 Cc Blood Contained	First Blood, Second Blood,	
	Mg	Mg
Sugar	139	162
Nonprotein nitrogen	223	253
Urea	166	193
Uric acid	11.3	15.6
Creatinin	12.6	13.3
Creatin		8.4

#### NECROPSY REPORT

Dr J. Jay Keegan reports as follows on the necropsy:

The necropsy findings were essentially negative except in the kidneys and heart. The kidneys were slightly smaller than normal. The capsule stripped easily leaving a finely granular and mottled surface. The cortex was distinctly thinned, measuring less than 5 mm in thickness in most regions. There was not clear distinction between cortex and medulla. The entire cut surface was mottled with red and gray. There was increased resistance to section. Microscopically, the chief lesion appeared in the interstitial tissue and in the blood vessels. There was a rather patchy increase of dense fibrous interstitial tissue without inflammatory cell infiltration, and the arterioles in all regions showed a marked thickening of the entire wall, with frequent hyaline degeneration and occlusion of the lumen. There was no cellular infiltration of the vessel walls and no marked hyperplasia of the intima. There was a moderate hyperplasia of the endothelium of the glomerular capillaries, but no inflammatory cell infiltration. Hyaline degeneration was frequent and occasionally there appeared ruptured capillaries with hemorrhage into Bowman's capsule and into the proximal convoluted tubules. Bowman's capsule was not thickened and the glomerular tuft not unduly lobulated. The pathology in the kidney is interpreted as chiefly vascular and interstitial rather than inflammatory, glomerular or tubular. The changes in the entire kidney might be interpreted as primarily vascular, but as in all such cases the value of the deduction would be questionable.

The heart showed a marked hypertrophy of the left ventricle, normal valves, and a few degenerated intimal plaques in the ascending aorta.

Sections of the liver showed nothing abnormal in this organ.



The results which we discussed in detail in the foregoing pages are summarized in the accompanying table

The study of the hippuric acid synthesis which we carried out with several normal and pathologic subjects leads us to the following considerations. In the tests with normal subjects we found that the addition of benzoic acid, calling on the kidney for an increased effort, has evidently a stimulating action on that organ. In our tests we not only recovered in twenty-four hours the full amount ingested but an appreciable excess, and, furthermore, the hippuric acid elimination, even in the next twenty-four hours, exceeded that found during the fore-period. In the pathologic subjects this is quite different. Here the ingestion of an extra amount of benzoic acid or its salt led to an output of benzoic acid or of its conjugation product—hippuric acid, more or less below the expected quantity. Besides, the excretion of both total benzoic and hippuric acid for the second twenty-four hour period after the ingestion (i. e., from twenty-four to forty-eight hours later) was less than in the preliminary period. It seems, therefore, probable that the pathologic kidney not only fails to accomplish the task of synthesis imposed on it, but in the effort it actually becomes partially exhausted or fatigued.

The elimination of benzoic acid or of its salts from the body follows very rapidly. Appreciable quantities are excreted within six hours and even in the pathological cases the largest amount may pass through the kidney in the first few hours. It is remarkable that on diets very poor in benzoic acid content the hippuric acid output in the urine remains relatively high. Benzoic acid must be, therefore, continually produced in the intestine and absorbed into the circulation. Kingsbury and Swanson<sup>18</sup> found the daily excretion of about 17 gm hippuric acid in a normal person on a mixed diet. When the diet was changed to one consisting of milk, cream, cheese, rock candy, i. e., one eminently poor in benzoic acid, the hippuric acid output diminished to about 0.7 gm but the significant thing is that for forty-eight hours after the change had been made the hippuric acid excretion still remained quite high. In at least two of our patients (Cases 10 and 11) with persistent constipation, we found it rather difficult to reduce the benzoic acid output by a restriction to a diet of milk and toast. We found it necessary to give this diet for forty-eight hours preceding the test, but even then the urine in Case 11 with the more pronounced and severe intestinal trouble could not be made entirely free from unconjugated benzoic acid. The experience with our patients has suggested the possibility that intestinal putrefaction may in some way be associated with hippuric acid elimination, and particularly with the free benzoic acid in the urine. Weyl and Anrep<sup>9</sup> noted in febrile animals that the proportion of free benzoic acid increases in that condition, and, further-

# RESULTS OF ANALYSIS MADE ON EIGHT PATIENTS

RESULTS OF ANALYSIS												
No of Cases	Clinical Diagnosis	Blood				Urine			Tests of Kidney Function			Remarks
		Mg per 100 Cc			Sugar	Daily Output, Cc	Average Specific Gravity	Albumin, per Cent	Hippuric Acid Test			
		N	P	N					Phenol-sulphone-phthalein, per Cent	Per Cent of Benzoic Acid Recovered	Per Cent of Hippuric Acid Recovered	
4	Chronic diffuse nephritis	91	48	18	800	1.024	+++	45	77	76	2.4 gm sodium benzoate administered in water Benzoic and hippuric acid determined in 24 hour urine	
5	Cardiorenal with albuminuria retinitis	120	65	45	2,500	1.010	0.08	15	59	58	2.4 gm sodium benzoate administered in water Benzoic and hippuric acid determined in 24 hour urine	
6	Cardiorenal	100	61	45	1,020	1.013	0.12	40	88	83	2.4 gm sodium benzoate administered in capsules Benzoic and hippuric acid determined in 24 hour urine	
					520	1.017			77	62	2.0 gm benzoic acid given in capsules Benzoic and hippuric acid given in capsules Milk	
					380	1.014			{15 55}	{14 50}	2 gm benzoic acid determined after 6 and 24 hours Milk and toast diet	
7	Chronic interstitial nephritis	98	117	65	1,000	1.008	0.1	10	76	72	2.4 gm sodium benzoate administered in water Benzoic and hippuric acid determined in 24 hour urine	
					1,820				{55 77}	{65 70}	1.2 gm sodium benzoate administered on two consecutive days Benzoic and hippuric acid determined in 24 hour urine	
8	Cardiorenal	110	18		780	1.011	+	50	67	53	2.4 gm sodium benzoate administered in capsules Benzoic and hippuric acid determined in capsules	
					830	1.017	+		87	79	2 gm benzoic acid given in capsules	
					1,800	1.010	+		{81 84}	{73 71}	2 gm hippuric acid determined in capsules made on hippuric acid given in capsules and toast diet	
					1,340	1.012	0.2	15	96	74	2 gm benzoic acid given in capsules Benzoic and hippuric acid determined in 24 hour urine	
9	Chronic diffuse nephritis		98	74	54	1,340		35	{81 100}	{76 95}	2 gm benzoic acid given in capsules Benzoic and hippuric acid determined in capsules Benzoic and hippuric acid given in capsules	
10	Cardiorenal		109	76	18	2,900	1.006	0.18	{80 91}	{74 81}	2 gm benzoic acid given in capsules Benzoic and hippuric acid determined in 6 and 24 hour urine Milk and toast diet	
					2,200	1.009					Determinations made in capsules Milk and toast diet	
11	Chronic diffuse nephritis		112	59	83	2,150	1.011	0.16	9	{33 100}	{28 91}	2 gm benzoic acid given in capsules Milk and toast diet
					2,150	1.010			{23 81}	{16 63}	2 gm benzoic acid given in capsules Milk and toast diet	

more, that the excess of unconjugated benzoic acid was not due to a lack of glycol as it did not diminish upon the addition of glycol to the food. In all of our patients except one (Case 5) the free benzoic acid in the urine following ingestion of benzoic acid or its salt increased markedly. We believe this to be the reason why Kingsbury and Swanson<sup>18</sup> thought the hippuric acid synthesis to be complete in nephritics, because they did not actually determine the free benzoic acid, regarding it a negligible quantity and assuming that it will not vary from the normal after the absorption of a large dose of the acid or its salt. Our analyses give no support to this assumption, and, as was already pointed out previously, their conclusion applies only to the total benzoic acid output in the urine, and not to the hippuric acid synthesis. In this connection it is well to note that in several of our patients (Cases 9, 10 and 11) the complete amount, or very nearly so, of the benzoic acid administered was recovered in twenty-four hours, while only from 63 to 95 per cent of the possible hippuric acid was synthesized in the same time. It is not improbable that Kingsbury and Swanson's patients were also of this type. This may explain why they recover practically 100 per cent of the administered benzoic acid, except that it is erroneous to identify all of this with its conjugation product, the hippuric acid.

Surveying the results with the patients under our observation we are inclined to believe that the elimination of free benzoic acid has been particularly marked in the nephritics and to a less extent in the cardiorenal cases. We appreciate, of course, that a larger number of patients would have to be examined before this could be definitely established.

Before leaving the subject of the free benzoic acid in the urine we wish to relate one particular instance, because we realize that criticism would be directed most vigorously against these results. One of us (S. M.) had taken the usual dose of benzoic acid but for some undiscoverable reason he experienced great discomfort shortly afterward. There was a strong burning sensation in the bladder and also during micturition. Although practically the full amount of benzoic acid consumed was eliminated in six hours, the free benzoic acid portion increased from 0.024 gm. in the preliminary urine to 0.256 gm. in the next six hours and most of this was passed soon after the benzoic was taken. The urine was intensely acid, and judging by the burning sensation and by the fact that the membrane of the bladder was so severely irritated that the urine was full of mucous shreds (there was no albumin), this must have been due to benzoic acid and not its salts. We have not been able to find out the cause of the disturbance which this test occasioned, especially as the other tests performed with the same subject were free from all unpleasant accompaniments. In fact, the test repeated a few days later was very successful and none of the symptoms described above occurred.

Another point which should be noted is that the patients arrange themselves into two groups as regards the elimination of benzoic acid in one group (Cases 9, 10 and 11) from 74 to 95 per cent is synthesized to hippuric acid in twenty-four hours, while the entire amount, or nearly so, of the administered benzoic acid appears in the urine, in the other group (Cases 4 to 8) from 59 to 88 per cent of the benzoic acid ingested has been recovered. Since we followed the benzoic and hippuric acid elimination in the urine for forty-eight hours after the administration of the benzoic acid, we are certain that this is not simply due to delayed excretion in these patients. The fact that the full amount of benzoic acid was not recovered would naturally lead one to suppose that either a part of the ingested benzoic acid has been conjugated in some other form, for instance, as a glucosid with glycuronic acid or in some other form and thus escaped detection. Dakin,<sup>24</sup> even when from 5 to 6 gm of sodium benzoate was given several days in succession, found no evidence that the benzoic acid undergoes oxidation, and he found only trifling amounts of glycuronic acid derivatives in the urine. It is possible, of course, that a process which in the normal organism is of slight significance may assume much greater importance under pathological circumstances. Unfortunately, we did not attempt to solve this problem by direct experimentation and can therefore offer no valid data at present for the elucidation of this point.

#### GENERAL CONCLUSIONS AND SUMMARY

In normal persons benzoic acid, administered either as the acid or its salt is completely synthesized to hippuric acid and the kidney is stimulated to enhanced activity. In nephritic and cardiorenal patients the synthesis is never complete and the kidney is apparently fatigued by the excessive exertion.

The benzoic acid passing in the urine is not all conjugated with glycol to form hippuric acid. A variable portion appears as the uncombined acid or as its salts. The unconjugated part of the benzoic acid can be reduced to an entirely negligible amount on a diet of milk and toast. Following the ingestion of a large dose of benzoic acid or sodium benzoate the free benzoic acid in the urine invariably increases, though to a very variable degree in different individuals. The increase is particularly great in patients with a definite kidney affection.

In all the patients which we examined the per cent of hippuric acid synthesized in twenty-four hours, following the ingestion of a standard dose of benzoic acid or sodium benzoate, ranged from 53 to 95 per cent, while from 59 to 100 per cent of the benzoic acid administered

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<sup>24</sup> Dakin, H. D. The Fate of Sodium Benzoate in the Human Organism. *J. Biol. Chem.* **7** 103, 1910.

could be recovered in the urine. In one group of patients, the recovery of benzoic acid has been almost the same as in normal subjects, but the hippuric acid synthesis was less than in the normal owing to the fact that a large amount of the benzoic acid was excreted in unconjugated form. In another group of patients both the elimination of total benzoic and of hippuric acid falls much below that in the normal subject. The free benzoic acid in the urine following a dose of the acid is apparently greater in the nephritic than in the cardiorenal cases.

Clinically, the method will in all probability not find extensive application or favor because it involves much work, and in order to secure reliable results the patient's regimen must be supervised very closely. Besides, the determinations require the strict care and precaution of the usual quantitative chemical analysis, a condition which the ordinary clinical laboratory does not satisfy. The test carried out with the same patient does not always yield quantitatively similar results which makes their proper interpretation still more difficult.

In conjunction with other renal function tests, the hippuric acid synthesis and the elimination of the benzoic acid may serve a very useful purpose. From our long experience with the method we would suggest that in performing the test for diagnostic purposes the following routine procedure should be observed. The patient should be on an exclusive diet of milk, cream, cheese, sugar with a liberal allowance of water, at least one day before the test is made. The patient should pass urine immediately before the substance is administered. It is preferable to give the necessary dose (2 gm benzoic acid or 2.4 gm sodium benzoate) in gelatine capsules as this eliminates any loss through incomplete solution or possible spilling when the solution is taken by the patient, especially when he is in a reclining position in bed. The urine collected for six hours after the substance had been taken should be analyzed according to the method described in the beginning of the paper for both the free and conjugated benzoic acid (hippuric). A second urine sample for eighteen hours should also be collected, thus completing a twenty-four hour urine after the benzoic administration, and analyzed in the same way. Alkalinization should be discontinued for the period of the test to prevent the possibility of the urine becoming alkaline. The urine samples should be properly preserved with thymol and kept in a cool place before analyzed. A general correction of 0.2 gm hippuric and 0.14 gm benzoic acid for every six hours may be applied and the amount of benzoic and hippuric acid recovered in the six and in the twenty-four hour period calculated from the experimental data.

It gives us great pleasure to express our appreciation to the staff of the medical ward of the University Hospital for their faithful and friendly cooperation. We are particularly indebted to Dr J. Jay Keegan for his unremitting interest in the work and the many courtesies so generously extended to us.

# EDEMA ASSOCIATED WITH MODERATE BICARBONATE ADMINISTRATION DURING CONVALESCENCE FROM PNEUMONIA<sup>1</sup>

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Sellards<sup>1</sup> showed that in normal persons the administration of from 5 to 10 gm sodium bicarbonate is sufficient to turn urine alkaline, while in patients suffering from acidosis a greater amount is required. Indeed, Palmer reports patients suffering from uremia who received 112 gm sodium bicarbonate and still excreted acid urine. Further investigations by Palmer and Van Slyke<sup>2</sup> demonstrated that in normal men the urine becomes more alkaline than the blood ( $p_H = 7.4$ ) when the plasma bicarbonate exceeds  $71 \pm 5$  volumes per cent. Of the ten pathologic cases which they studied during sodium bicarbonate administration, most showed a higher plasma bicarbonate level than this, before the urine became more alkaline than the blood. They conclude, therefore, that in pathologic conditions there is danger of giving "unnecessary and perhaps injurious" amounts of sodium bicarbonate if administration is continued until the urine turns alkaline, and that the administration should be discontinued when the blood bicarbonate becomes normal.

The case which we are here describing is one in which after administration of sodium bicarbonate in amounts of from 5 to 6 gm per day for several weeks, an alkali excess in the blood was observed, despite a continuously acid urine. The bicarbonate retention was accompanied by a water retention of 11 kilograms with an edema which involved the lungs and appeared to be responsible for abnormalities of clinical importance in the respiration (rapid, very shallow breathing, and intense cyanosis). Bicarbonate administration was stopped, and the patient was kept in an atmosphere with 40 per cent of oxygen to relieve the anoxemia. The kidneys began almost at once to excrete bicarbonate, the edema gradually disappeared, and the respiration became normal.

## REPORT OF CASE

*History*—A married woman, aged 47 years, had with the exception of frequent attacks of sinus infections, for the past several years enjoyed good health.

<sup>1</sup> From the Hospital of the Rockefeller Institute for Medical Research.

1 Sellards, A W. Johns Hopkins Hosp Bull **23** 289, 1912.

2 Palmer, W W, and Henderson, L J. Arch Int Med (Aug) **12** 153, 1913, Palmer, W W, and Van Slyke, D D. J Biol Chem **32** 499, 1917.

She had noticed, however, that for almost six years slight exertion caused shortness of breath Feb 17, 1922, while on the train en route to New York, she had a chill Two days later she was confined to bed in a New York hotel with a temperature of 102 F and respirations of 30 to the minute The following day there were râles in the left lower chest, pain on deep breathing, and blood tinged sputum, from which pneumococcus Type 1 was isolated The condition thereupon ran the course of a lobar pneumonia with areas of consolidation in the upper halves of both lower lobes February 26, a heavy trace of albumin was noted in the urine, but no casts were seen During the critical part of her illness, there was well marked cyanosis, and respirations were shallow and reached 60 per minute

*Course*—After having had 1,000 c.c. of antipneumococcus serum, her temperature gradually fell, and remained between 100 and 101 F, her respirations at 40 per minute March 20, or a little more than a month after the onset of the acute illness, moderate edema of the left foot and ankle appeared Beginning about March 24, the patient did not seem so well, the cyanosis increased, the urinary output diminished, and generalized edema of the body appeared, respirations were shallow, and the patient was slightly irrational There was a heavy trace of albumin in the urine which was acid to litmus and contained many hyaline and granular casts This condition persisted for the following five days, when the patient was first seen by one of us

TABLE 1—OXYGEN AND CARBON DIOXID CONTENT OF BLOOD AND  $p_H$  OF PLASMA AND URINE

Arterial Whole Blood							
Oxygen Content, Volume per Cent	Oxygen Capacity, Volume per Cent	Oxygen Unsaturatation		Carbon Dioxid Content		Plasma, pH	Urine, pH
		Volume per Cent	Per Cent of Capacity	Total, Volume per Cent	Bicarbonate, Milli- molecular		
8.24	13.49	5.25	39	70.6	30.0	17.49	6.2

*Treatment*—She was admitted to the Hospital of the Rockefeller Institute for the purpose of investigating the cause of her cyanosis and dyspnea The patient was put on a Gatch bed in a fairly upright position, which somewhat relieved her respiratory distress The fluid intake was restricted to 1 liter per day, and she was given a salt-free diet No medication was prescribed The following day, blood was drawn from the radial artery and analyzed for its oxygen and carbon dioxide content, and the plasma  $p_H$  The results of this analysis are shown in Table 1

*Discussion*—The oxygen figures indicated an oxygen unsaturation in the arterial blood sufficient to account for the cyanosis Lundsgaard<sup>3</sup> has shown that when the average capillary unsaturation, estimated as the mean between the arterial and venous exceeds about 65 volumes per cent of oxygen, cyanosis usually becomes visible We were not able to obtain venous blood from this patient, because of her extensive edema, but with a normal fall of 5 volumes per cent from arterial to venous oxygen, the mean capillary unsaturation would be  $5.25 + 2.5 = 7.75$  volumes per cent

The bicarbonate concentration of 30 millimolecular in the whole blood as drawn was 50 per cent above the normal average of 20

millimolecuar for blood with  $p_H$  7.49<sup>4</sup>. The  $p_H$  of 7.49,<sup>5</sup> though not certainly above extreme normal range, was near the upper extreme. The condition of the acid-base balance was, therefore, one of alkali excess, or bicarbonate retention. The acid urine ( $p_H$  6.2) indicated a pathologic inability to excrete the bicarbonate.

Since alkali excess can hardly occur in man without alkali administration, inquiry was made concerning previous alkali therapy, and it was ascertained that during the thirty-five days of her illness prior to admission to the hospital, she had been given approximately 200 gm sodium bicarbonate, or on an average of 5.7 gm per day, not in itself an excessive dose. All the while the patient had been excreting a urine acid to litmus.

*Oxygen Therapy*—Because of the pronounced arterial unsaturation, oxygen therapy seemed indicated. Accordingly the patient was put in the oxygen chamber and exposed to an atmosphere containing 40 per cent of oxygen. Relief from symptoms was immediate and striking. Cyanosis disappeared, and the respiratory rate fell. At the time of admission to the chamber the chief physical signs and symptoms were intense cyanosis, rapid breathing, generalized anasarca and hydrothorax. After twenty-four hours in the oxygen chamber, the patient was removed for the purpose of getting a roentgenogram of her chest. The recurrence of cyanosis and subjective discomfort were as prompt and striking as their disappearance had been, and on return to the chamber they again vanished.

Table 2 gives the blood gas analyses and the pulmonary ventilation on four successive days, the first and third with the patient breathing atmospheric air, the second and fourth with the patient breathing an atmosphere containing twice the normal oxygen concentration. The subsequent findings during convalescence are also brought out in this table.

In both instances of exposure to 40 per cent oxygen, the minute volume of pulmonary ventilation diminished, due to a fall in the respiratory rate, the depth of individual respirations (tidal air) remaining unchanged. In both instances the arterial unsaturation disappeared, and in both instances there was a marked diuresis. Whether this diuresis was real, due to an improved oxygenation of kidney tissue, or whether it was apparent and due to a lessened water elimination through the lungs consequent to the diminished minute volume of pulmonary ventilation, we cannot be sure.

4 Van Slyke, D. D. J. Biol. Chem. 49:158, 1921 (Fig. 2).

5 The blood  $p_H$  examinations were made by the method recently described by Cullen and checked electrometrically.



TABLE 2—SHOWING DATA AS TO RESPIRATION, ARTERIAL BLOOD AND URINE

Date	Day of Disease	Respiration				Arterial Blood				Urine				In-spired Air, per Cent Oxygen	Body weight in Kilos	Estimated $\text{N}_2\text{HCO}_3$ Output, Gm			
		Respirations per Min	Minute Volume, Liters	Tidal Air, Cc	Residual Air, Liters	Vital Capacity, Liters	Lung Total Capacity, Liters	Oxygen Content, Volume per Cent		Oxygen Capacity, Volume per Cent	Unsaturated		Carbon Dioxide Content, Volume per Cent						
								per Cent	Volume per Cent		Volume per Cent	Per Cent of Capacity					Fluid Intake, Cc	Fluid Output, Cc	Reaction to Litmus
March 30	40	46	8.06	176				8.24	13.49	5.25	39	70.6	7.49	905	670	Acid	6.2	69.6	21
March 31	41	32	5.53	170				14.40	14.30		0	81.0	7.53	805	1,490	Acid		67.0	40
April 1	42	46	8.14	178				10.91	14.20*	3.39	24	78.3	7.52	1,000	790	Alkaline		66.7	21
April 3	44	24	4.49	184				13.90	14.20	0.30	2.1	77.1	7.45	880	1,753	Alkaline	7.9	65.5	40
April 6	47	37	8.73	234		0.64								1,000	2,095	Alkaline		62.8	21
April 8	49	22	6.30	293	0.50	0.83	1.48							1,000	1,560	Alkaline		62.0	21
April 13	54	20	8.65	430	1.00	1.07	2.07	14.35	15.65	1.30	8.3	52.3	7.49	1,000	931	Acid		58.6	21
April 19	60													1,000	1,145	Acid			
April 29	70													1,500	1,055	Acid	5.4	0.03	21
May 9	81	20	10.88	538	0.98	1.52	2.50	13.01	13.56	0.55	4.0	50.6	7.45						21
May 10	82																		21
May 12	84	20	10.50	540	1.10	1.60	2.70												21

\* Assumed

*Loss of Edema*—The patient was kept in the oxygen chamber continuously for the five days following April 1. April 6 she was removed, when cyanosis no longer persisted under atmospheric conditions. During this time her weight fell from 69.6 kilos to 62.9 kilos, her twenty-four hour fluid excretion often more than doubling her intake. Tissue edema rapidly decreased. April 1 her urine, which had been acid to litmus and contained many casts, became alkaline and no casts were to be seen. It remained alkaline to litmus until April 9, when it again became acid without a recurrent appearance of casts. The hydrogen ion concentration of the urine is shown in Table 2. Progressive loss of weight continued until April 12, when the weight curve became flat and the patient was apparently in water balance.

With the disappearance of fluid from the chest, the tidal air gradually increased, and the patient's lung volume, which had been much reduced, due no doubt to compression of the lungs by hydrothorax, and to pulmonary edema, also augmented as shown in Table 2.

TABLE 3—RESULTS OF RENAL FUNCTION TESTS WITH NORMAL VALUES SHOWN

	Observed	Normal
Blood urea nitrogen, gm per liter	0.0825	0.15-0.25
Urea index (Austin, Stillman and Van Slyke)	53	45-115
Plasma chlorids, gm per liter	5.76	5.62-6.20
Plasma proteins		
Albumin, per cent	3.9	5.0
Globulin, per cent	3.7	3.0
Total protein, per cent	7.6	8.0
Globulin — Total protein	48	30
Phthalein, 1st hour per cent	34	
Phthalein, 2d hour per cent	14	
Total per cent	48	60-80

*Kidney Function*—An effort to account for the alkali retention in this case on the basis of renal insufficiency was made by a study of the patient's renal function, which was done on April 19 by Dr. Geoffrey Linder of the Staff of the Rockefeller Hospital. In summary, it may be said that the phthalein excretion showed a value below normal, and the plasma globulin formed a somewhat higher proportion of the total protein than normal, as frequently seen in cases of nephritis with edema and albuminuria. The renal functional tests made are given in Table 3 with accompanying normal values.

The dilution and concentration test showed a normal water excreting function.

*Disappearance of Alkalosis*—Examination of the arterial blood carbon dioxide content and  $p_H$  values shown in Table 2, reveals some interesting facts. The 70.6 volume per cent carbon dioxide at the time of admission increased during the next day to 81.0 volumes per cent. This was accompanied by an increase in  $p_H$  from 7.49 to 7.55, and

signifies, we believe, a transport of base from the tissues to the blood. The next two observations show a drop in carbon dioxide volume per cent to 78.3 and 77.1 successively, and in  $p_H$  to 7.52 and 7.45. Just at this time the urinary  $p_H$ <sup>6</sup> which had been 6.2 became 7.9, indicating the passage of retained base from the blood stream through the kidneys. This change was accompanied by the enormous loss of tissue edema mentioned above. Assuming the urinary unbound carbon dioxide to be 4.2 volumes per cent, Gamble<sup>7</sup> has calculated the bicarbonate content of urine from the  $p_H$ . A rise such as this from  $p_H$  6.2 to  $p_H$  7.9 represents an increase in sodium bicarbonate elimination from approximately 0.2 gm per liter to 8 gm per liter.

Apparently when the body retains bicarbonate, it retains sufficient fluid to keep the osmotic concentration in body fluids normal. With cessation of bicarbonate administration and improvement of kidney function, in this case, fluid and base were eliminated simultaneously. It is possible that the relief from anoxemia was in some degree responsible for the improved kidney function.

#### SUMMARY AND CONCLUSIONS

The case studied was one of lobar pneumonia, in which an average of 57 gm sodium bicarbonate had been given for a period of thirty-five days prior to admission to the hospital. The patient showed intense cyanosis with marked oxygen unsaturation of the arterial blood, rapid breathing, anasarca and hydrothorax, and evidence of alkalosis (blood  $p_H$  7.55). Oxygen therapy largely relieved cyanosis and dyspnea. Immediately thereafter the patient began to excrete retained base and water. Whether this was more than a coincident relationship and just what rôle the salt free diet played in dehydration we are unprepared to say. Diminution of edema was accompanied by gradually increasing lung volume and return to normal type of respiration. No definite impairment of kidney function could be established other than shown by a slightly reduced phthalein excretion. At the time of discharge from the hospital, the patient's blood oxygen, carbon dioxide content, and  $p_H$  were normal, the urine  $p_H$  was normal, and the urine was free from albumin and casts. The case is reported to show that definite untoward results may follow the administration of sodium bicarbonate, and to point out the character of certain of these untoward results.

6 The urine was collected without precaution against exposure to air and colorimetric hydrogen ion concentration determinations made on freshly voided specimens.

7 Gamble, J. L. *J. Biol. Chem.*, **51**: 295, 1922.

## PROTEIN FEEDING AND HIGH BLOOD PRESSURE

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This study was undertaken for the purpose of acquiring more experimental data than can be found in the literature on the subject of the relation of protein intake to high blood pressure. As far as can be judged from a study of the subject, opinions are, in the main, based on empirical clinical impressions or on personal opinion without evidence of any sort. How widely these opinions vary may be illustrated by reference to the articles of Hamman<sup>1</sup> and Mosenthal<sup>2</sup> from the same clinic in 1917. As a matter of fact, Mosenthal<sup>3</sup> in 1920 commented on the absence of actual experimental data and was one of the first to attempt an experimental study on human beings.

No discussion of any phase of the hypertension problem can be complete without a review of the more recent studies of hypertension in relation to the diseases most often associated with it,—myocarditis, arteriosclerosis and nephritis. Whereas up to ten or fifteen years ago hypertension was considered a symptom of arteriosclerosis or chronic nephritis, evidence is steadily accumulating to prove the existence of primary or so-called essential hypertension, which, in its earlier stages at least, is entirely free from demonstrable lesions of the cardiovascular renal systems (Christian,<sup>4</sup> Pratt,<sup>5</sup> Vaquez,<sup>6</sup> O'Hare,<sup>7</sup> Harpuder<sup>8</sup>). The hyperpiesis of Clifford Allbutt,<sup>9</sup> the hypertension of the menopause

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\*From the Medical Clinic and the Nelson Morris Memorial Institute for Medical Research of the Michael Reese Hospital

1 Hamman, L. M. *Clinics N. America* **1** 155 (July) 1917

2 Mosenthal, H. O. *M. Clinics N. America* **1** 101 (July) 1917

3 Mosenthal, H. O. *Am. J. M. Sc.* **160** 808 (Dec.) 1920 also *M. Clinics N. America* **5** 1139 (Jan.) 1922

4 Christian, H. *Oxford Medicine* **3** 751

5 Pratt, J. H. *J. A. M. A.* **73** 331 (Aug. 2) 1919

6 Vaquez, H. *Bull. de l'Acad. de med.* **81** 283 (March 11) 1919

7 O'Hare, J. P. *Am. J. M. Sc.* **159** 369 (March) 1920

8 Harpuder, K. *Deutsch. Arch. f. klin. Med.* **129** 74 (April) 1919

9 Allbutt, C. *Diseases of the Arteries Including Angina Pectoris* London, 1915

may be cited as instances. Although the words essential hypertension may be poorly chosen, they give a significance to the condition in distinguishing it from the hypertension with nephritis and in centering attention on hypertension as the earliest demonstrable symptom.

That patients with essential hypertension may later in life develop cardio-renal complications affords no justification for the conclusion that the primary cause of the high blood pressure lies in the organ or organs which secondarily show evidence of disease. Study of histories of patients and careful continuous clinical observation will reveal many patients with hypertension of fairly high grade and yet with no evidence of myocardial degeneration, arterial change or disturbance in kidney function. Moschcowitz<sup>10</sup> has brought forward evidence—experimental and clinical—suggesting, if not actually proving, that even in cases of frank nephritis hypertension may be the earliest demonstrable symptom.

Furthermore, attention may be directed to the fact that, in certain conditions leading to hypertension with nephritis, the high blood pressure precedes the nephritis. The menopause hypertension which has been so carefully studied by Hopkins<sup>11</sup> and by Riesman<sup>12</sup> belongs to this group. Observation on older diabetics who later develop severe nephritis justifies the statement that hypertension precedes nephritis—although it may not always precede arterial changes. In hyperthyroidism of certain types it is not uncommon to find hypertension without nephritis. In the toxemias of pregnancy which later develop into the “kidney of pregnancy,” we have observed that hypertension precedes demonstrable renal disturbance (Ives<sup>13</sup>). There is also plenty of evidence that arteriosclerosis without increased blood pressure occurs as a clinical and pathologic entity.

The newer studies on renal function are supposed to uncover the earliest manifestations of renal insufficiency, and such studies as have been made on patients with hypertension show that the presence of albumin and casts may not indicate true renal disease (Rappleye,<sup>14</sup> O'Hare,<sup>15</sup> Lankhout<sup>16</sup>). In another field of observation, the study

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10 Moschcowitz, E. Hypertension with Minimal Renal Lesions, *J A M A* **77** 1075 (Oct 1) 1921, *Am J M Sc* **159** 517 (April) 1920, *Clinical and Anatomic Relations in Chronic Nephritis*, *Arch Int Med* **26** 259 (Sept) 1920.

11 Hopkins, A. H. *Am J M Sc* **157** 826 (June) 1919.

12 Riesman, David. Hypertension in Women, *J A M A* **73** 330 (Aug 2) 1919.

13 Ives, R. F. *Am J M Sc* **160** 61 (July) 1920.

14 Rappleye, W. C. *Boston M & S J* **179** 441 (Oct 3) 1918.

15 O'Hare, J. P. *Boston M & S J* **182** 345 (April 1) 1920.

16 Lankhout. *Nederl Tijdschr v Geneesk* **1** 1439 (April 24) 1920, abstr., *J A M A* **75** 440 (Sept 7) 1920.

of nitrogen retention in the blood, further evidence may be found of a lack of correlation between blood pressure findings and kidney function (Williams<sup>17</sup>)

The effect of any form of therapy on blood pressure should be studied on the basis of the statements just made. The changes in blood pressure found in any given case must be correlated and evaluated in relation to the presence or absence of other signs of disease. It is futile to compare the effect of protein on the blood pressure of a patient showing advanced renal disease and albuminuric retinitis with the same degree of hypertension in a woman showing merely menopausal hypertension.

We have been skeptical about the dangers of protein in hypertension even in patients with definite cardiovascular or renal complications. Without concrete experimental proof it seemed that although

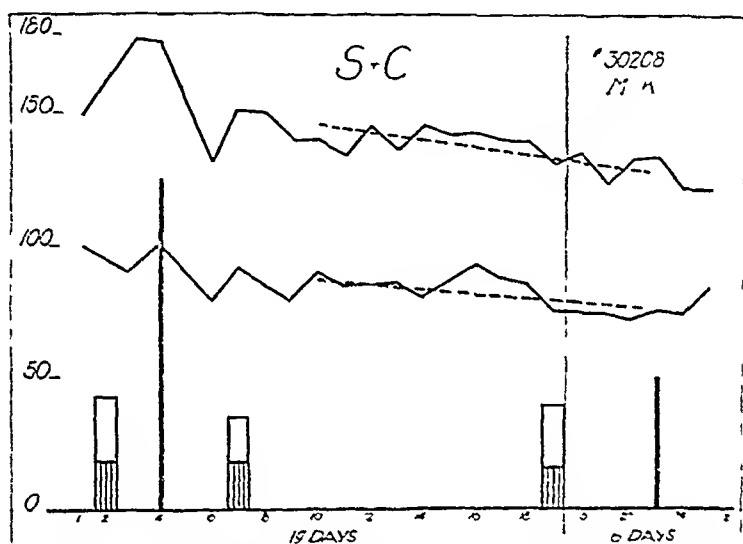


Chart 1—During a nineteen-day period of protein intake of 125 gm including soup and coffee daily (S+C of chart) there is a drop in pressure. During the first six days there is an initial drop to 140/85, after which the pressure remains stationary. Perhaps it would be more accurate to say that in this case, the high protein diet with soup and coffee did not raise the pressure. A final six-day period of protein intake of 50 gm shows a slight further drop.

The charts are drawn to the same scale. The vertical numbers indicate the blood pressure in millimeters of mercury; protein intake in grams; nonprotein nitrogen and urea nitrogen in milligrams per hundred cubic centimeters. The horizontal figures show the number of days in each period. The thin black vertical lines block off each period; the heavy vertical lines represent the amount of protein intake for the period corresponding with the numbers on the left. The vertical rectangles represent blood nonprotein nitrogen and urea nitrogen in milligrams per hundred cubic centimeters. Systolic and diastolic pressures are shown by the solid horizontal lines. The broken lines are drawn between points representing the average pressure for each period.

17 Williams J. L. The Total Nonprotein Nitrogen Constituents of the Blood in Arterial Hypertension, *Arch Int Med* 27:748 (June) 1921.

changes did follow protein restriction such changes were more readily explained by other changes in the patients' mode of living. In many instances results followed correction of habits uncovered by what Cobb<sup>18</sup> calls "personality study"—an effort to get at the fundamental psychic as well as physical background of the patient (Christian<sup>4</sup>). The effect of emotion on blood pressure is much more easily demonstrated than the effect of protein food. We were unable to convince ourselves that patients were harmed by protein. Excess of any kind of food seemed decidedly more injurious than a moderate amount of protein in a well balanced diet. Flatulence and digestive disturbances often resulted from substitution of carbohydrate and fat, and these

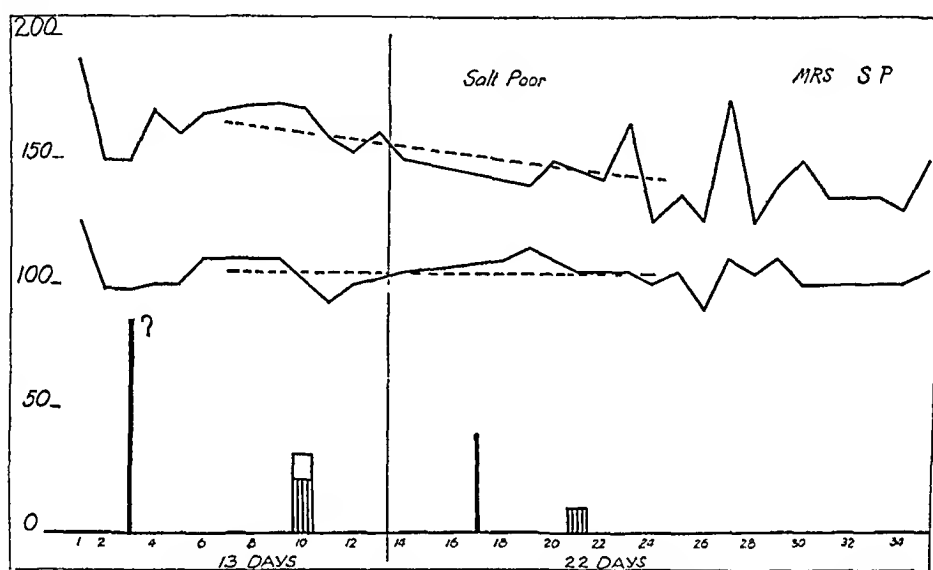


Chart 2—Marked daily variations are shown, but there is little change in the pressure in the two periods of 85 gm and 40 gm, respectively

disturbances together with weight increase we believed more harmful than protein. Our clinical observations were not in accord with the opinions expressed among others by Hamman,<sup>1</sup> Meara,<sup>19</sup> Bishop,<sup>20</sup> Musser<sup>21</sup> and Snow,<sup>22</sup> but were in agreement with the clinical observations and experiments of Moschocowitz<sup>10</sup> and Mosenthal.<sup>3</sup> From an experimental standpoint it is interesting to note that although Newburgh<sup>23</sup> was able to show that large amounts of meat damaged the kidney he states that no blood pressure changes occurred in his experiments

18 Cobb, S. M. *Clinics N America* **3** 1137 (Jan) 1920

19 Meara, F. S. M. *Clinics N America* **2** 1 (July) 1918

20 Bishop, L. F. *J A M A* **73** 332 (Aug 2) 1919

21 Musser, J. *New York M J* **112** 570 (Oct 16) 1920

22 Snow, W. B. *New York M J* **105** 5 (Jan 6) 1917

23 Newburgh, L. H. *The Production of Bright's Disease by Feeding High Protein Diets*, *Arch Int Med* **24** 359 (Oct) 1919

## EXPERIMENTAL DATA

In order to add further data to the scant amount found in the literature, we attempted to attack the problem by a series of intensively studied experiments on a small number of patients. The method of procedure was as follows. Patients with hypertension and with varying degrees of damage to the cardiovascular or renal systems were placed in the hospital. They were not kept at complete bed rest but were allowed to walk around the ward and corridor. Successive periods of observation lasting approximately from seven to thirty days were instituted, the diet measured and controlled for each period.

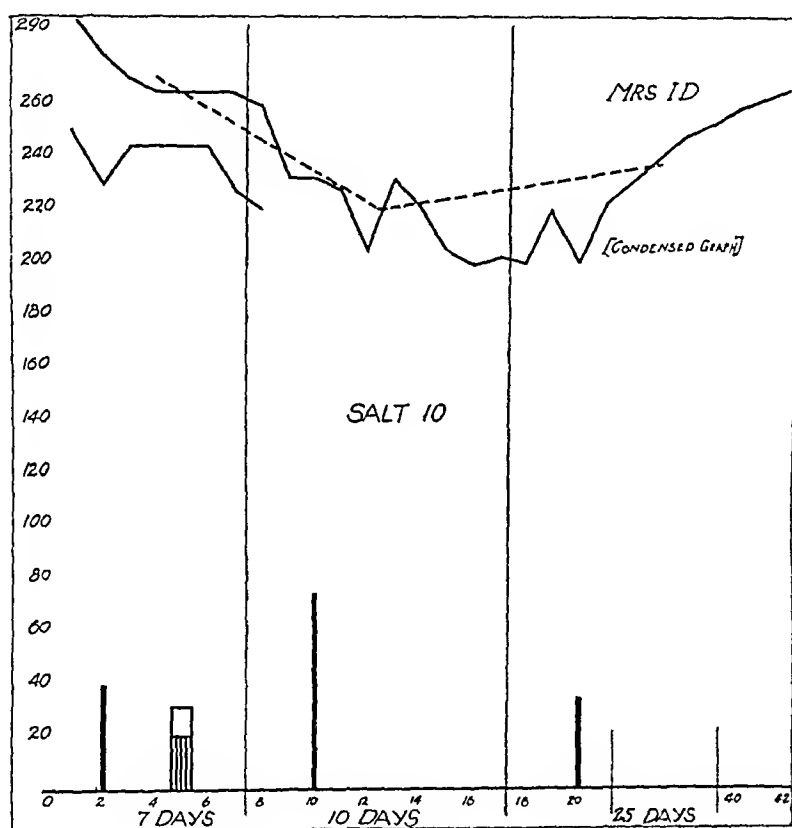


Chart 3—Definite slight drop in pressure on admission is shown, and a level of 245 for six days of protein intake, 40 gm, a marked drop when protein was raised to 75 gm and salt (10 gm) added, and a subsequent steady rise when protein was limited to 35 gm for twenty-five days.

Blood pressure readings were taken twice daily—between 8 and 9 a m and between 5 and 6 p m. The same mercury sphygmomanometer was used for all readings. The patient was always in the same position and the same arm was used. If changes in interns' schedule meant a change in observer, personal sources of error were controlled by joint readings during the transition period.

Clinical observation of the condition of the patient with special reference to his heart, blood vessels and kidneys were supplemented by studies of blood chemistry and kidney function which were done as



far as possible to correspond with the dietary periods. Routine work on the blood included nonprotein nitrogen, urea nitrogen, uric acid, sugar and cholesterol on admission, with repeated observations on nonprotein nitrogen, urea nitrogen and sugar. The Mosenthal renal test meal was done at the beginning of the period of observation. The phenolsulphonaphthalein excretion was studied usually at two different times. The urine studies included amount passed in twenty-four hours, specific gravity, presence of albumin and casts, total nitrogen, urea nitrogen, sodium chlorid, titrable acidity, and relation of monosodium phosphates to disodium phosphates<sup>24</sup>. With later cases special atten-

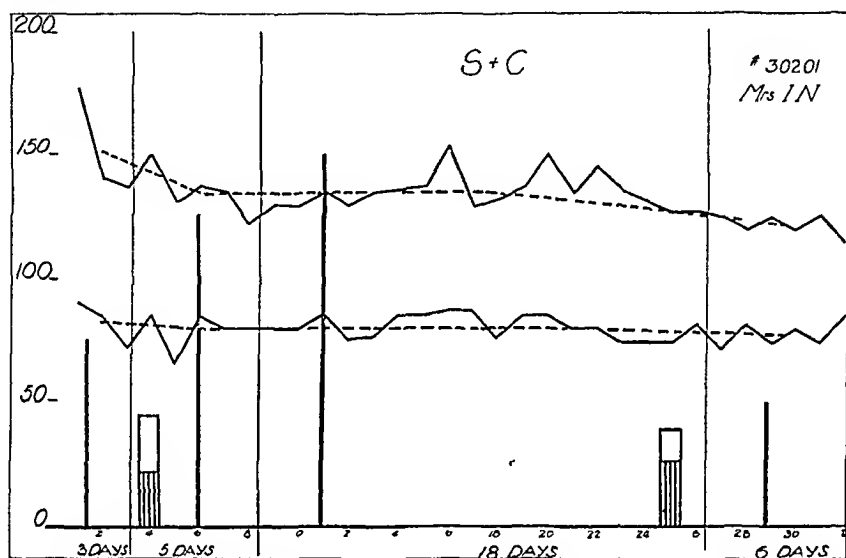


Chart 4—Blood pressure during a preliminary three-day period of administration of 75 gm protein dropped from 175/85 to 138/75. During a second period of five days, with protein intake at 125 gm, the pressure continued to drop. A period of eighteen days with protein at 150 gm, and soup and coffee, follows. At first the pressure rises slightly, but it drops again toward the end of the period, making an average the same as for the preceding period. A final period of six days with protein intake at 50 gm shows a continuation of the drop noted at the end of third period, the average being 122 as compared with 136 for the third period. It is to be noted that despite the wide range of systolic pressure, the diastolic remains practically constant.

24 The methods used were as follows: Blood—Nonprotein Nitrogen, Urea Nitrogen and Uric Acid, Folin, O, and Wu, H. *J Biol Chem* **38** 81, 1919. Sugar—Folin, O, and Wu, H. *J Biol Chem* **41** 367, 1920. Cholesterol—Bloor, W R. *J Biol Chem* **23** 317, 1915.

Urine—Mosenthal, H O. Renal Function as Measured by the Elimination of Fluids, Salt and Nitrogen and the Specific Gravity of the Urine, *Arch Int Med* **16** 733 (Dec.) 1915. Total nitrogen—Folin, O, and Denis, W. *J Biol Chem* **26** 473, 1916. Urea nitrogen—Folin, O, and Denis, W. *J Biol Chem* **26** 501, 1916. Chlorid—Harvey, S C. The Quantitative Determination of the Chlorids in the Urine. *Arch Int Med* **6** 12 (July) 1910.

Acidity—Folin, O. *Am J Physiol* **13** 45, 1905.  $\frac{\text{NaH}_2\text{PO}_4}{\text{Na}_2\text{HPO}_4}$  Leathes, J B. *Brit M J* **2** 165, 1919.

tion was paid to the search for red blood cells (Newburgh<sup>23</sup>) (It may be stated here that in none of our cases was protein increase followed by the appearance of red blood cells in the urine) By this procedure we hoped to classify our cases with regard to kidney damage and also to follow any possible effect of dietary changes on the kidneys and blood

The results are shown in the form of a graphic chart for each patient studied In order to simplify the charts urinary data are not included, but important facts in relation to kidney function are given in the protocols to the charts One daily blood pressure is charted—the average of the two readings Variations in systolic blood pressure

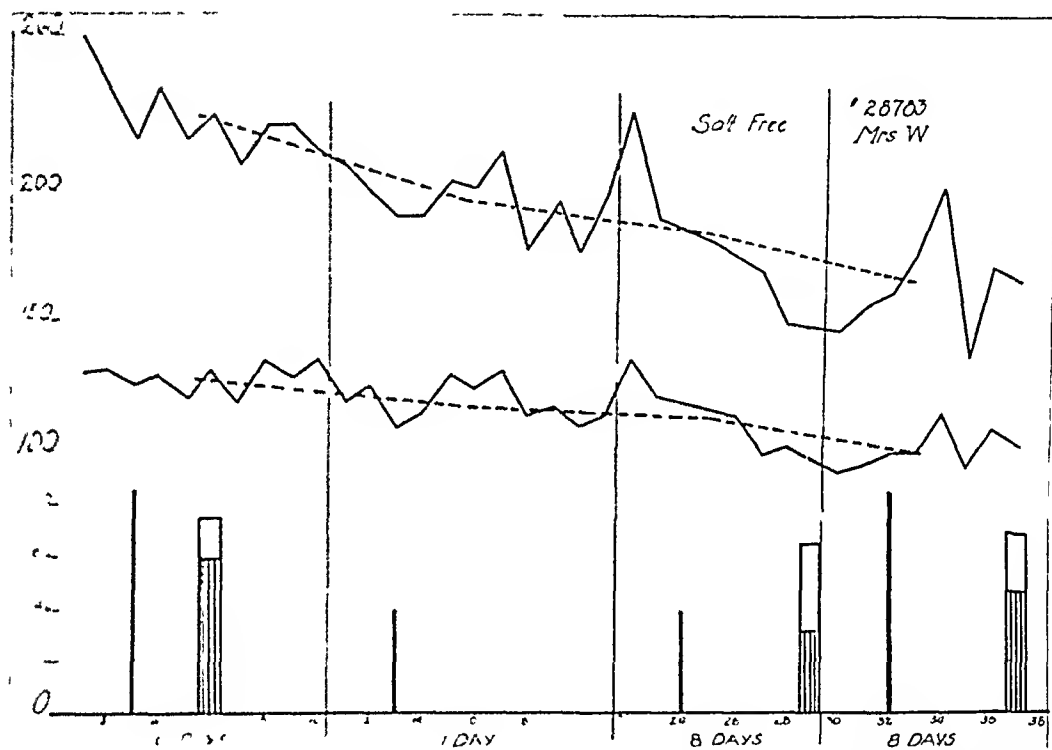


Chart 5—A steady drop in both systolic and diastolic blood pressures is shown, with no apparent relationship to protein intake The daily variations are in some spots as high as the difference between the maximum and minimum period averages The high figures for blood nonprotein nitrogen and urea are in this instance only slightly influenced by the protein intake The eight-day salt-free period with protein at 50 gm is followed by a drop in pressure, but a still further drop is noted in a succeeding eight-day period with protein at 85 gm and no limitation of salt

between morning and evening on the same patient were at times as great as 60 mm mercury and were usually not constant On one day the morning pressure was higher than the evening pressure, on the next day the reverse was true Marked and rapid changes seemed to be associated with emotional disturbances A good night's rest would be followed by reduced pressure, a nocturnal disturbance in the ward would be indicated by high readings the following morning

## REPORT OF CASES

CASE 1—A K (No 30208), male, aged 54 Well up to two months ago when he had pains all over his body, especially in the lower extremities, dyspnea on exertion

*Physical Examination*—Arteries soft, heart normal in size, no irregularities, no murmurs, coarse scattered râles Urine at no time showed albumin or casts Specific gravity, 1020-1024 Mosenthal test showed no nocturia, no fixation Phenolsulphonephthalein excretion 60 per cent in two hours Uric acid of blood, 16 mg, sugar 0.13 per cent, urinary nitrogen and sodium chlorid excretion normal

*Diagnosis*—Chronic bronchitis and hypertension

CASE 2—Mrs S P (No 31231), aged 41 Five years ago, following a pelvic operation, she had edema of the feet, albumin and casts She was in this hospital where a diagnosis of chronic nephritis and hypertension was made From 1916 to 1921 she was in comparatively good health, but very nervous suffering from headache, palpitation, disturbances of vision She

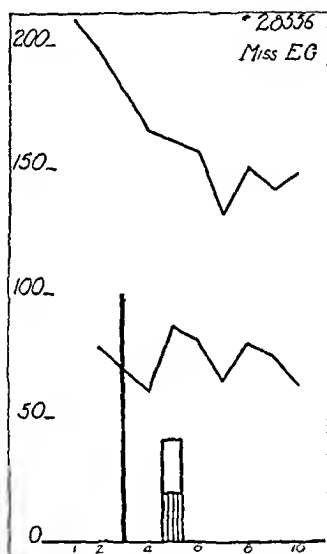


Chart 6—A pronounced drop in systolic pressure from 210 to 132 is shown, with no marked change in diastolic pressure, during a period of seven days, with protein intake at 100 gm Previous to this period, the intake was at the minimum This marked change could be associated with a synchronous change in the patient's nervous condition, and with such an interpretation the change in systolic blood pressure would represent a vasomotor phenomenon

came to the admitting room of the hospital with these symptoms and with a blood pressure of 190/120 The urine was negative and she was admitted to the hospital as a case of "essential hypertension"

*Physical Examination*—Entirely negative, except for tenderness along the colonic region At no time during her hospital stay was albumin or casts found Mosenthal test meal showed specific gravity fixed at 1020-1022, no nocturia Phenolsulphonephthalein excretion, 65 per cent in two hours Excretion of urinary nitrogen, urea, and of sodium chlorid was normal in relation to intake The blood chemistry as shown in the chart was normal

*Diagnosis*—Hypertension and colitis

CASE 3—Mrs I D (No 18182), aged 47 Sick about three years with "pains all over," palpitation, dyspnea, headaches

*Physical Examination*—Hypertrophied heart, large liver. Urine showed a trace of albumin, occasional hyaline and granular casts, specific gravity usually around 1027. This patient was studied before the present investigation was begun, and her chart is shown for comparison.

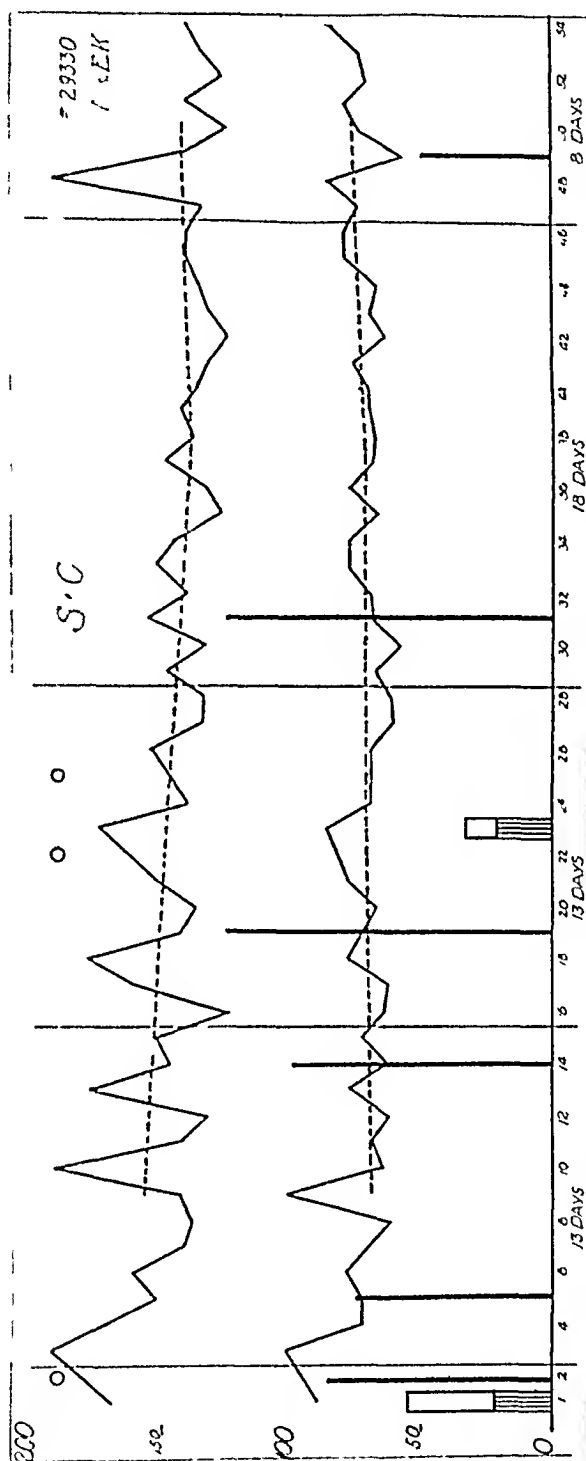


Chart 7—A steady drop in pressure for the entire stay of fifty-four days in the hospital. Protein intake varied from 50 to 125 gm., and for one period of eighteen days, soup and coffee were freely given.

*Diagnosis*—Hypertension, chronic myocarditis, chronic nephritis.

CASE 4—Mrs I N (No 30201), aged 42. Sick about ten years, but does not give a history of value. She complains of indefinite symptoms, and it is difficult to uncover the relation between the glycosuria and the other conditions.

*Physical Examination*—Hypertrophied heart, slightly thickened peripheral blood vessels, slight edema of ankles. Urine showed occasional trace of albumin, no casts, specific gravity varied between 1022 and 1026. Sugar in small amounts was present (0.09 per cent) only on very high carbohydrate feeding. Mosenthal test meal, night urine 450 cc, day 500. Phenolsulphonephthalein excretion, 67 per cent in two hours. Excretion of urinary nitrogen, urea, and sodium chlorid was normal in relation to intake. Blood sugar varied from 0.13 to 0.17 per cent, nonprotein nitrogen, urea nitrogen of blood above normal.

*Diagnosis*—Hypertension, nephritis, myocarditis, diabetes mellitus (?)

CASE 5—Mrs W (No 28783), aged 52. Sick four years, pain in chest, feet, hands, cough.

*Physical Examination*—Peripheral blood vessels firm. Heart normal. Urine showed usually trace of albumin and occasional granular cast. Phenolsulphonephthalein excretion in two hours, 43 per cent. Mosenthal test meal fixation of specific gravity but no nocturia. Excretion of nitrogen and urea always low. Sodium chlorid excretion normal. Blood nitrogen products high (Chart 5).

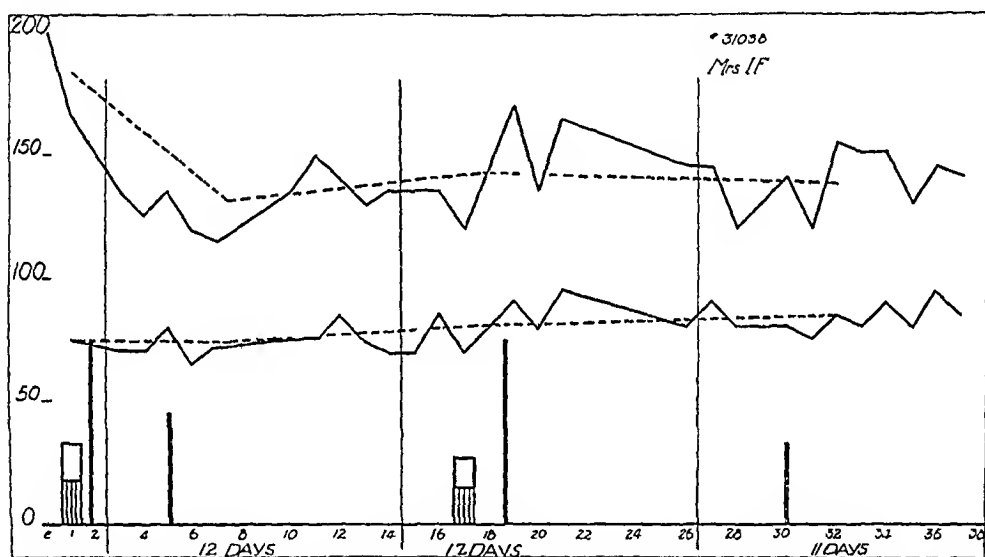


Chart 8—An initial two-day period of protein intake 75 gm, is associated with a drop in pressure from 200 to 125 after which, the average is between 132 and 140, while the daily variations are marked. Protein intake varied between 35 and 75 gm, and a rough relation is seen between the protein and blood pressure changes. Owing to the fact that the patient was diabetic, we did not care to change the protein intake too much. Unlike the other charts, this chart shows a steady rise in diastolic pressure.

*Diagnosis*—Hypertension, chronic nephritis.

CASE 6—Miss E G (No 28556), aged 53. Complains of attacks of severe abdominal pain, constipation, anorexia, nervousness. For three days she has been practically starving on account of the fear of abdominal pain.

*Physical Examination*—Very nervous, tachycardia, increased reflexes, gall-bladder tenderness. Her pressure when first seen was 210. Heart and blood vessels were normal. (After a careful examination on admission, she was urged to eat freely of a mixed diet containing 100 gm protein.) Urine on admission showed a trace of albumin, which disappeared at once. Excretion of nitrogen and urea not abnormal. Other kidney function tests not made.

*Diagnosis*—Hypertension, menopause, cholelithiasis.

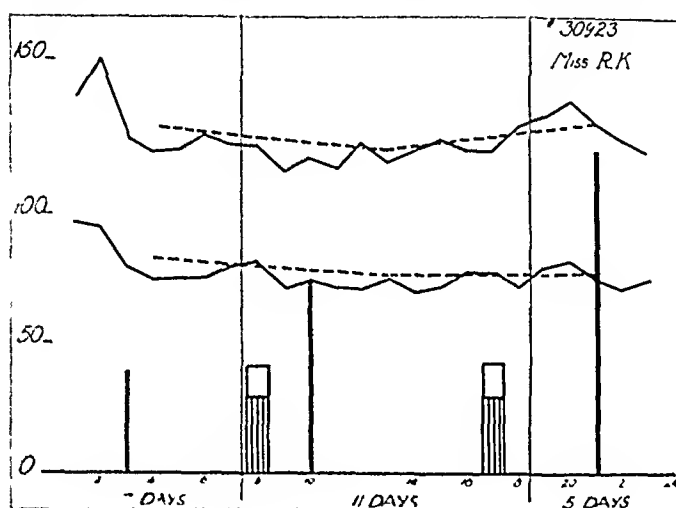


Chart 9—This patient who suffered from a progressive nephritis and hypertension was placed successively on three periods of protein feeding, 50, 75 and 125 gm, respectively. The pressure here shows a slight but definite tendency to rise with increased protein intake.

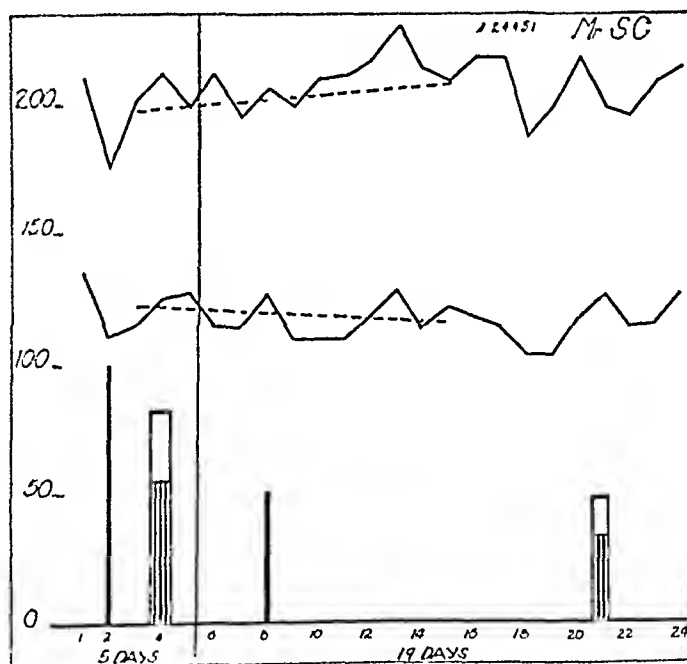


Chart 10—A drop in protein intake from 100 to 50 gm, which was sufficient to reduce the nonprotein nitrogen and urea of the blood, was, nevertheless, associated with a rise in blood pressure.

CASE 7—Mrs E K (No 29330), aged 57 Duration ten years, pains in shoulder, headache, dyspnea on exertion and precordial pains Onset of glycosuria doubtful

*Physical Examination*—Enlarged heart, extrasystoles, no hardening of peripheral arteries Urine at no time showed albumin or casts Sugar appeared when carbohydrate intake was excessive Excretion of nitrogen and of sodium chlorid was normal Phenolsulphonethaleim excretion, 49 per cent in two hours Mosenthal test meal showed night urine 950, day urine 520, with specific gravity varying from 1.012 to 1.022 Urine this day showed sugar Blood sugar varied from 0.168 to 0.25 per cent

*Diagnosis*—Hypertension, myocarditis, diabetes mellitus

CASE 8—Mrs I F (No 31038), aged 47 Diabetes ten years' duration High blood pressure discovered recently

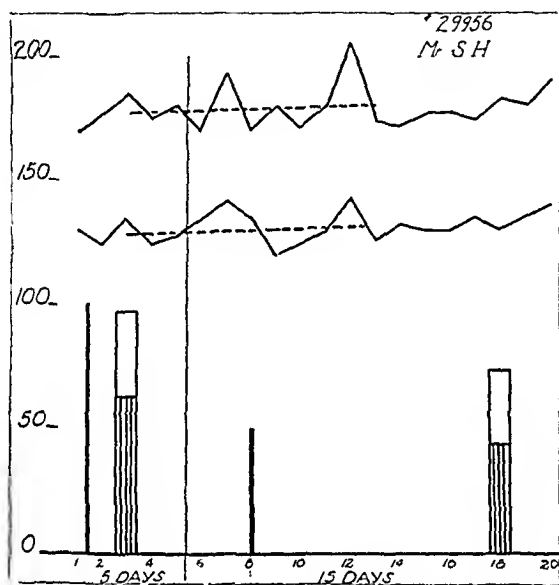


Chart 11—The findings in Case 11 were similar to those obtained in Case 10 Chart 10 should be compared for details

*Physical Examination*—Râles and some dulness upper lobe of both lungs Urine at no time contained albumin or casts Glycosuria with carbohydrate intake in excess of tolerance Mosenthal test meal normal Blood sugar on admission, 0.40 per cent Nitrogen normal

*Diagnosis*—Hypertension, diabetes mellitus, pulmonary tuberculosis (?)

CASE 9—Miss R K (No 27697), aged 18 In hospital five months ago with parenchymatous nephritis of nine months' duration Much edema and pallor Large amount of albumin, hyaline and granular casts Blood pressure, from 150 to 170 Between the two hospital admissions she was under dispensary observation and given increased protein (Diet not measured in this period) This was apparently followed by lessened albuminuria and edema Blood pressure slowly but steadily rising

*Physical Examination*—On return to hospital, examination showed typical appearance of a pale edematous nephritic Urine always contained albumin, hyaline and granular casts Phenolsulphonethaleim excretion 48 per cent in two hours Mosenthal test meal showed night urine of 690, specific gravity varying between 1.016 and 1.024 Nitrogen excretion normal salt retained

*Diagnosis*—Hypertension, subacute nephritis

CASE 10—S G (No 29942), aged 33 A typical case of advanced nephritis with organs showing marked degenerative changes

*Diagnosis*—Advanced chronic nephritis with hypertension, retinitis, etc

CASE 11—S H (No 29956), aged 42 This case was identical with Case 10 and showed the same results from feeding

### CONCLUSIONS

The study here reported supplemented by other ambulant cases, justifies the following conclusions

1 In patients with hypertension and with slight or no impairment of renal function marked variations in blood pressure occur Such variations bear no relation to the intake of protein food

2 In such cases no damage to renal function and no increase in nonprotein nitrogen or urea nitrogen of the blood was found to follow protein feeding up to 150 gm daily

3 In three such cases strong stock soup and coffee given daily did not increase blood pressure

4 In cases of frank progressive nephritis with hypertension, a diminution of protein intake sufficient markedly to lower the figures for blood nonprotein nitrogen and urea did not cause lowering of the blood pressure

5 The experiments here reported add further evidence to that already accumulated to prove the existence of a clinical entity characterized by a primary hypertension They further suggest that variations in blood pressure in this condition are the direct result of vasomotor disturbances



# RELATION BETWEEN HEMOGLOBIN, CELL COUNT AND CELL VOLUME IN THE VENOUS BLOOD OF NORMAL HUMAN SUBJECTS \*

H C GRAM, M D, AND A NORGAAARD, M D

COPENHAGEN

In spite of extensive work on these subjects, it cannot be said that the relation between hemoglobin, cell count and cell volume in normal blood has ever been clearly stated. The reason for this must be sought, first, in that most authors in examining normal blood limited their research to one or two of these factors, secondly, in that there exists a considerable confusion in the expression of hemoglobin. Even when 100 per cent hemoglobin is defined as the color corresponding to an oxygen capacity of 18.5 per cent, the question is not solved. Recently Van Slyke and Stadie<sup>1</sup> have drawn attention to the fact that the Haldane method for determining the oxygen capacity of the blood may give results which are markedly too low (as low as 10 per cent). Thus we get the explanation of the phenomenon that Haldane<sup>2</sup> and his collaborators have found 18.5 per cent oxygen capacity to be the average in the blood of healthy men, while this figure in later researches has proved to be nearer an average between normal men and women. A too low hemocolorimeter standard called 18.5 per cent oxygen is the explanation of the results obtained by Haldane<sup>3</sup> and by one of us (Gram<sup>4</sup>) which would make the normal color index nearer 0.9 than 1, and the ratio  $\frac{\text{hemoglobin per cent}}{\text{volume per cent}} = 2.14$ <sup>5</sup>.

These hemoglobin values do not tally with those obtained by most other observers, as, for instance, Bie and Møller<sup>6</sup>. Recently one of us<sup>7</sup> published a critical survey of these matters.

As already mentioned, we have in former papers dealt with the ratio  $\frac{\text{hemoglobin per cent}}{\text{volume per cent}}$  and found that this was fairly constant in most diseases.

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\* From the University medical clinic of Prof. Knud Faber.

1 Van Slyke, D. D., and Stadie, W. C. *J. Biol. Chem.* **49**, 1, 1921.

2 Haldane, J. S. *J. Physiol.* **26**, 497, 1900.

3 Haldane, J. S., and Smith, L. *J. Physiol.* **25**, 331, 1899.

4 Gram, H. C. *Ugeskr. f. Læger* **82**, 1543, 1920.

5 Norgaard, A., and Gram, H. C. *Compt. rend. soc. biol.* **84**, 151, 1921, *Dansk selskab f. int. med.*, 1920, p. 65.

6 Bie, V., and Møller, P. *Ugeskr. f. Læger* **74**, 749, 817, 878, 1913.

7 Gram, H. C. *Ugeskr. f. Læger* **84**, 215, 1922.

If this is true, one may approximately calculate one of these values when the other is known. One may also use determinations of cell volume to check the hemoglobinometer standard. The same would be the case, if the ratio  $\frac{\text{hemoglobin per cent}}{\text{cell count}} = 1$ , i. e., the color index, was fairly constant in normal subjects.

One might then standardize a hemoglobinometer, for instance, to 100 per cent hemoglobin = 5 millions of normal cells per cubic millimeter. It stands to reason that one would have to make very exact cell counts repeatedly on the blood of several normal subjects.

On account of the extreme clinical importance of these relations we have considered it expedient to take up the question with the most exact methods at our disposal.

In order to minimize the error in our methods, we have used only venous blood secured by puncturing a cubital vein and stabilized with hirudin.

As no manufactured product was available, this hirudin was made by diving and powdering leeches' heads, extracting with water and precipitating with alcohol. The dried product was very effective, part of a milligram being sufficient to prevent coagulation for days in more than 10 c.c. of blood. The salt content of the hirudin was infinitesimally small, so that the blood corpuscles were not subjected to osmotic shrinkage. Thus, the use of admixture of isotonic citrate or oxalate solutions was avoided.

The blood was obtained from ten normal males and ten normal females. The male subjects were physicians, medical students and hospital porters; the female subjects were nurses and hospital servants. All subjects were physically sound and fit for their work.

The blood was taken into a small conical vessel closed by a rubber cork. After mixing it thoroughly with the dry hirudin, about ten glass beads were added in order to shake up the agglutinated and sedimented corpuscles before drawing off each specimen for analysis.

#### METHODS

The methods used were the following:

- 1 *Hemoglobin*—An Autenrieth and Königsberger hemoglobinometer with a good color wedge was used. Four dilutions in the proportion 20 + 1980 were made in all cases with the same pipet, using tenth normal hydrochloric acid. Ten readings were taken on each dilution after exactly ten minutes.

The average scale value for each patient was noted. For this hemoglobinometer we procured a curve of corrections based on a pre-

sumably reliable oxygen determination, so that we could express the scale values in terms of hemoglobin per cent, 100 per cent being defined as equaling an oxygen capacity of 18.5 per cent (first vertical column of Table 1)

On account of the uncertainty of oxygen determinations, we resolved to use still another standard based on the assumption made in calculating the color index, i. e., 100 per cent hemoglobin corresponds to 5 million normal corpuscles per cubic millimeter

At the end of our work we found that the average scale value in all twenty cases was 30.0055 Autenrieth, and the average cell count 5.0541, that is, according to the above assumption, 101.082 per cent hemoglobin

TABLE 1—DATA ON TEN NORMAL MALES

Age, Years	Hemoglobin, per Cent		Cell Volume, per Cent	Cell Count, Millions per C Mm	Color Index		Volume Index	Ratio Hb per Cent Vol per Cent	
	 100 per Cent 18.5 per Cent O <sub>2</sub>	 100 per Cent 5 Millions Normal Corpuscles per C Mm			 100 per Cent Hb 18.5 per Cent O <sub>2</sub>	 100 per Cent Hb 5 Millions Normal Corpuscles per C Mm		 100 per Cent Hb 18.5 per Cent O <sub>2</sub>	 100 per Cent Hb 5 Millions Normal Corpuscles per C Mm
42	118 00	117 26	48 75	5 900	1 00	0 99	0 96	2 42	2 41
27	116 50	116 10	50 00	5 911	0 99	0 98	0 98	2 33	2 32
20	115 87	115 37	47 75	5 754	1 01	1 00	0 97	2 43	2 42
36	110 87	110 42	46 50	5 504	1 01	1 00	0 98	2 37	2 37
22	108 00	107 40	46 69	5 464	0 99	0 98	0 99	2 31	2 30
37	108 50	107 96	46 80	5 405	1 00	1 00	1 01	2 32	2 31
20	105 40	104 88	47 08	5 307	0 99	0 99	1 03	2 24	2 23
30	104 75	103 96	42 88	5 167	1 02	1 01	0 97	2 44	2 42
24	104 12	104 29	44 56	5 272	0 99	0 99	0 98	2 34	2 34
22	96 38	95 62	42 38	4 854	0 99	0 98	1 02	2 27	2 26
Average	108 84	108 32	46 34	5 454	1 00	0 99	1 00	2 35	2 34
Maximum	118 00	117 26	50 00	5 911	1 02	1 01	1 03	2 44	2 42
Minimum	96 38	95 62	42 38	4 854	0 99	0 98	0 96	2 24	2 23

Since the scale value 102.08 represented 0 corpuscles and 0 per cent hemoglobin, the hemoglobin per cent could be calculated in each single case. These hemoglobin percentages will give an idea of the individual variations in the relation of the coloring power to the cell count. On being compared with the results won by the standardization to oxygen capacity, these hemoglobin percentages will give an idea as to whether the assumption made in calculating the index is fairly correct or not.

**2 Cell Count**—On each specimen four different dilutions and counts were made with Hayem-Jørgensen's liquid and Ellermann's separate pipets for blood and diluting fluid (10 and 1990 c mm). The pipets had previously been carefully calibrated with mercury, and the same pipets were used throughout our experiments. The Burkner-Turk

counting cell was used, twenty large squares being counted from each of the four dilutions. A subtraction of the white cell count was not made.

3 *Cell Volume*—The cell volume percentage was determined with a special hematocrit constructed after our designs by Jacob, Copenhagen. The frame carried four branches, into which the capillary tubes were fitted with a screw, the ends being closed by hard rubber plates. The length of the capillary tubes was 10 cm. divided into 200 gradations allowing readings of one fourth of a volume per cent. The tubes were carefully cleaned and dried, then filled with avoidance of air bubbles and

TABLE 2—DATA ON FIFTEEN NORMAL FEMALES

Age, Years	Hemoglobin per Cent		Cell Volume per Cent	Cell Count, Millions per C Mm	Color Index		Volume Index	Ratio Hb per Cent Vol per Cent	
	100 per Cent Hb 5 per Cent O <sub>2</sub>	100 per Cent Hb 5 Millions Normal Corpuscles per C Mm			100 per Cent Hb 15.5 per Cent O <sub>2</sub>	100 per Cent Hb 5 Millions Normal Corpuscles per C Mm		100 per Cent Hb 15.5 per Cent O <sub>2</sub>	100 per Cent Hb 5 Millions Normal Corpuscles per C Mm
27	102.25	101.68	43.00	5.054	1.01	1.01	0.99	2.38	2.36
32	103.00	99.13	40.42	4.832	1.01	1.03	0.97	2.47	2.46
35	99.75	98.24	41.42	4.937	1.01	1.01	0.98	2.41	2.40
37	97.37	96.78	42.08	4.731	1.03	1.02	1.04	2.31	2.30
31	99.25	97.41	42.00	4.600	1.05	1.04	1.06	2.29	2.27
39	102.00	99.52	39.42	4.548	1.01	1.01	1.01	2.33	2.32
35	99.12	98.91	38.91	4.475	1.01	1.00	1.01	2.31	2.29
28	92.38	88.69	39.88	4.552	0.98	0.97	1.02	2.24	2.22
22	89.28	88.68	38.81	4.455	1.00	1.00	1.01	2.30	2.28
28	95.00	87.49	39.33	4.360	1.01	1.00	1.05	2.24	2.22
Average	99.45	97.85	40.53	4.654	1.015	1.01	1.01	2.33	2.32
Maximum	102.25	101.68	43.00	5.054	1.05	1.04	1.06	2.47	2.46
Minimum	88.00	87.49	38.81	4.360	0.98	0.97	0.97	2.24	2.22

fitted into the frame, which was rotated at high speed ( $> 3,000$  revolutions a minute). The centrifuging was continued till the corpuscular column became transparent throughout its length. This lasted generally between 1 hour and  $1\frac{1}{2}$  hours. All four tubes gave similar results, and no subtraction of the white cell volume was made, as the borderline against the red cells was not always clearly defined.

The values found in our tables are averages of the four determinations of each sort made on every single specimen. In a few of the early cases, however, only two volume determinations were carried out.

In preparing our material for tabulation we have placed the men and women apart, giving for each group the average, maximum and minimum of both groups lumped together.

As to the indices and quotients put forward in these tables, we must call attention to the fact that the average index is the relation between the respective average values found, while the maximum and minimum are those found in the table and do not correspond to the maximum and minimum of hemoglobin, cell count and volume

The values to be found in the tables, besides the age of the subjects are, from left to right, the following

1 Hemoglobin percentage calculated from scale values<sup>8</sup> on the assumption 100 per cent hemoglobin = 18.5 per cent oxygen

2 Hemoglobin percentage calculated from scale values on the assumption 100 per cent hemoglobin = 5 millions of normal corpuscles (101.082 per cent = 5.0541 millions [Table 3])

TABLE 3—SUMMARY OF DATA ON TEN MALES AND TEN FEMALES

	Hemoglobin, per Cent		3	4	Color Index		7	Ratio Hb per Cent Vol per Cent	
	1	2			5	6			
	 100 per Cent O <sub>2</sub> 18.5 per Cent	 100 per Cent 5 Millions Normal Corpuscles per C Mm			 100 per Cent Hb 18.5 per Cent O <sub>2</sub>	 100 per Cent Hb 5 Millions Normal Corpuscles per C Mm		 100 per Cent Hb 18.5 per Cent O <sub>2</sub>	 100 per Cent Hb 5 Millions Normal Corpuscles per C Mm
Average	101.64	101.08	43.43	5.051	1.00	1.00	1.00	2.34	2.33
Maximum	118.00	117.26	50.00	5.911	1.05	1.04	1.06	2.47	2.46
Minimum	88.00	87.49	38.81	4.360	0.98	0.97	0.96	2.24	2.22

3 Cell volume per cent

4 Cell count in millions per cubic millimeter of blood

5 Colorimetric index calculated from the first named hemoglobin percentage by the formula  $I = \frac{Hb}{Er} \frac{\%}{20}$ , Er being the cell count in millions per c mm

6 Colorimetric index calculated from the second hemoglobin percentage<sup>2</sup> according to the same formula

7 Volumetric index (volume index) This index gives an idea of the variations of the normal relation between cell volume and cell count According to Table 3 this relation is 42.96 volume per cent = 5 millions normal corpuscles per cubic millimeter (i. e., 43.43 volume per cent = 5.0541 millions)

8 The Autenrieth scale values being individual to the apparatus used, we have not considered it practical to publish them

Formerly one of us calculated this index from the formula  $\text{Volume I} = \frac{\text{Volume per cent } 0.12}{\text{Er}}$  (Gram<sup>9</sup>), but in this case we use the more exact formula  $\text{Volume I} = \frac{\text{Volume per cent } 0.1164^{10}}{\text{Er}}$  Er being the cell count in millions per cubic millimeter

8 The ratio hemoglobin per cent Volume per cent calculated from the first hemoglobin percentage<sup>1</sup>

9 The ratio hemoglobin per cent Volume per cent calculated from the second hemoglobin percentage<sup>2</sup>

Of course, this quotient might be expressed also as an index (I colorvolumetricus), which would vary between 1.06 and 0.95, but for practical purposes the ratio has been chosen

### CONCLUSIONS

1 In these tables are found, first, the normal boundaries<sup>11</sup> of hemoglobin percentage, cell volume and cell count in normal male and female subjects. The volume determinations, on the whole, agree very well with those obtained by other authors (Bie and Møller<sup>6</sup> and Gram<sup>7</sup>). As to the cell counts, it is generally admitted that the old values, 5 millions for men and 4.5 millions for women, are incorrect, even though they are repeated with great regularity in physiologic and even clinical textbooks. The hemoglobin determinations agree astonishingly with those found by Bie and Møller,<sup>6</sup> but they are considerably higher than the values published previously by Haldane,<sup>2</sup> Haldane and Smith<sup>3</sup> and Gram.<sup>4</sup> This applies both to averages and to normal figures: the divergence being nearly 10 per cent. As already stated, these variations may safely be asserted not to be real but due to incorrect standardization of the hemoglobinometers used by the last named authors.

2 A comparison between the hemoglobin percentage calculated to 100 per cent = 18.5 per cent oxygen and 100 per cent = 5 millions normal corpuscles shows that the difference is very slight, being on the average only 0.56 per cent hemoglobin.

The ordinary assumption made in calculating the color index is nearly true, when our hemoglobinometers are standardized to 100 per

9 Gram, II C. Compt rend Soc de biol 49 264, 1921

$\frac{\text{Volume Percent}}{\text{I 1}}$

10  $\text{Volume I} = \frac{12.96}{5}$  This may also be expressed by introducing

the constant  $\frac{\text{Hb\% Vol \%}}{\text{Vol \%}} = 2.33$  in the formula used for calculating the color-index  $\text{Vol I} = \frac{\text{Vol \% } 2.33}{\text{Er } 20}$

11 Naturally, a larger series might show cases slightly exceeding these extremes

cent hemoglobin = 18.5 per cent oxygen capacity in an irreproachable way

If 100 per cent hemoglobin is defined as equaling 5 millions normal corpuscles per c mm the color index should be 1. The actual variations found in this very exact series of determinations ranges between 1.04 and 0.97, which is probably not more than may be expected from the unavoidable errors of the two methods involved. If only single determinations on each person are made, the error may easily be larger, so that in ordinary clinical work an index between 0.9 and 1.1 could not be called anything but normal.

3. A consideration of the volume index shows that in normal persons the cell volume varies nearly proportionally with the hemoglobin and cell count, that is, that the size and hemoglobin content of the red corpuscles is nearly constant. The range of variation of the volume index, however, is slightly larger than that of the color index, being 1.06 and 0.96. This may partly be due to a greater inaccuracy of the volume determinations, partly to the varying amounts of white cells having different individual volumes.

4. The ratio  $\text{Hb \%} / \text{Vol \%}$  averages 2.33 when 100 per cent hemoglobin means 5 millions normal cells (or nearly 18.5 per cent oxygen). In normal persons, however, a range of variations between 2.46 and 2.22 is found, this may partly find its explanation in the experimental error on the two determinations. The importance of this fairly constant ratio lies in the possibility of estimating the cell volume, when the hemoglobin is known, this may play a rôle in analysis of total blood and plasma won from blood stabilized with isotonic salt solutions. Caution is necessary in cases of jaundice, leukemia and chlorosis while the ratio determined agrees very well in cases of pernicious anemia.

5. The use of a good hematocrit may be advocated for studying and checking variations of cell count and hemoglobin content in normal subjects and of hemoglobin content in most pathologic cases. The cell volume determinations have the advantage of being less subjected to subjective errors than the other methods.

# TOXIC MANIFESTATIONS FOLLOWING THE ALKALINE TREATMENT OF PEPTIC ULCER<sup>1</sup>

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Sippy<sup>1</sup> has attributed the chronicity of ulcer to the corrosive action of gastric juice, and on this basis administered small amounts of alkali to the patient hourly, over a long period (from three to four weeks in the hospital and several weeks afterward). By a combination of powders—calcium carbonate, magnesium oxid, sodium bicarbonate and bismuth subcarbonate—in varying proportions, he was able completely to neutralize the gastric juice, and thereby to promote healing of the ulcer. He says, "It may be helpful to know that in rare instances it has required the equivalent of 30 grains (2 gm.) each of calcium carbonate and sodium bicarbonate, every hour, midway between feedings and every half hour after the last feeding until 9 p. m. to control the free acidity. He does not, however, discuss a certain group of cases in which it is difficult and almost impossible to control the acidity.

It has been our experience in this particular group, with one exception, that when an attempt is made to control the acidity, symptoms of toxemia usually appear.<sup>2</sup> Physicians who have used the alkaline treatment in a large group of cases have undoubtedly noted that some patients develop a distaste for milk, that they have headaches and sometimes vomit. But thus far, no one seems to have studied the etiology and symptomatology of the condition from the standpoint of blood chemistry.

MacCallum<sup>3</sup> was able to produce gastric tetany with associated toxic manifestations in dogs by mechanical pyloric obstruction. With the constant withdrawal of hydrochloric acid, the decrease in the chlorid of the plasma and the consequent increase in the alkali reserve became extreme. The electrical excitability of the nerve was heightened, twitchings were spontaneous, and usually the condition terminated fatally with convulsions. The lives of the animals could be prolonged by administering sodium chlorid.

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\* From the Section on Medicine of the Mayo Clinic.

1 Sippy, B. W. Gastric and Duodenal Ulcer, Medical Cure By an Efficient Removal of Gastric Juice Corrosion, *J. A. M. A.* **64** 1625 (May 15) 1915.

2 Hardt, L. L. Medical Management of Peptic Ulcer, *Ann. Med.* (In press).

3 MacCallum, W. G., Lintz, J., Vermilye, H. N., Leggett, T. H., and Boas, E. The Effect of Pyloric Obstruction in Relation to Gastric Tetany, *Bull. Johns Hopkins Hosp.* **31** 1, 1920.



From the patients with peptic ulcer who were observed in the Mayo Clinic from April 1, 1921, to April 1, 1922, forty-eight were selected for study. The diagnosis had been confirmed by roentgenograms in all. The forty-eight patients were classified in three groups, Group 1 consisted of sixteen patients who were treated for one week by hourly feedings of milk without alkali. They were then treated according to the usual Sippy method. This experiment was made for the purpose of determining whether or not the milk alone was a factor in causing the complicating symptoms. Group 2 consisted of sixteen patients who were placed directly on the Sippy treatment and remained normal throughout the course. Group 3 consisted of sixteen patients who showed toxic symptoms while under the Sippy treatment.

In virtually all cases a twelve-hour specimen of urine (night) was examined microscopically for blood, pus and casts and chemically for albumin and sugar. The specific gravity was estimated and the renal function was tested by phenolsulphonaphthalein return. Blood urea, creatinin and the carbon dioxide combining power of the plasma were also determined. These tests were repeated on the day before additional food or alkalis were given and again during the last week of treatment. If symptoms of toxemia developed, the laboratory data were again obtained. The patients in Group 3 had blood urea of 50 mg or more for each 100 c c. Creatinin determinations were not made unless the blood urea was 70 mg or more. In one case the blood chlorides were also determined during the period of toxemia.

#### RESULTS

The chemistry of the blood or urine was not affected in the "milk control" patients in Group 1. Similar results were obtained in Group 2.

The sixteen patients of Group 3 exhibited definite symptoms of toxicity. The incidence of this syndrome was found to be greater in men than in women. It is not probable that age plays a part in determining the liability of a patient to the development of adventitious symptoms while under treatment. The ages of the patients range from 24 to 66 years, the average being about 35 years.

The symptoms of intoxication are apt to arise at any time during the course of the treatment, within four or five days after the powders are given, not until the third or fourth week, or following the use of two or three additional 5 grain calcium carbonate powders. Patients whose gastric acidity persistently remains uncontrolled may show symptoms early. Occasionally, they have headache and slight nausea and, while further symptoms may follow, often the complaint disappears and the remainder of the course is without disturbing incidents.

*The Clinical Evidence of Toxicity*—The mode of onset and the subsequent symptoms are almost invariably the same in all patients of Group 3. Before the patients developed the more serious symptoms, they seemed unduly introspective and nervous. They were irritable and complained about trifles which they had overlooked previously. The first symptom to appear was a distaste for milk. When patients well established in their treatment began to complain that the milk was sour or distasteful, or that it left a bad taste in the mouth, other complications were expected to follow shortly. Milk is supplied to patients in 18 ounce bottles. Often patients complained that the second glass taken from the bottle seemed sour. Milk from these bottles was often tasted by a physician or attendant and found to be sweet and quite palatable. This symptom may be present three or four days before others develop. In some instances headaches come on almost simultaneously with the dislike for milk, and at this stage it is usually difficult to persuade the patients to take their powders. They are, however, not as distasteful to them as the milk.

Headache, an early symptom, is at first a dull feeling described as a sensation of tightness in the nape of the neck or the occipital region. The pain may become very severe, extending to the temporal area. At other times the headaches, dull, boring, throbbing, and intensified by each heart beat, originate in the frontal or temporal region. The headache persists through the entire syndrome, becoming more severe as the subsequent complaints arise. It is usually the last symptom to disappear.

With the increasing dislike for milk, nausea becomes pronounced and the patient vomits on making efforts to take food or even water. The vomiting may become alarming and is checked with difficulty usually only after repeated gastric lavage.

Dizziness is a common symptom, even in the milder cases. Patients first complain of vertigo and a light headedness when attempting to walk or move. If symptoms are marked, even turning the head from the pillow brings on marked vertigo and usually nausea and vomiting.

Aching pains in the muscles and joints was a common symptom, the distribution of the pain was indefinite and simulated that preceding influenza. Weakness, at first slight, became marked and, if measures of relief were not prompt, absolute prostration followed rapidly. Respirations became slow, the pulse slightly accelerated, the face flushed, and perspiration profuse. The patients lay in bed limp, apathetic, and very drowsy, and were roused with difficulty. When the symptoms reached the point of nausea and vomiting (with few exceptions), the alkalis were stopped and the patient was put on two-hour feedings consisting of milk, cereals, eggs, fruit juices, and meat broth. Within from twenty-four to forty-eight hours the symptoms

almost invariably disappeared. In six instances it was necessary to continue this treatment with small doses of alkali one hour before and one hour after meals, because toxic symptoms recurred following attempts to place the patients on the Sippy regimen with alkalis every hour.

*Laboratory Evidence of Toxicity*—During toxic manifestations the blood urea increased from 50 to 296 mg. for each 100 c c, the creatinin from 2 to 5 mg. The carbon dioxide in the normal patients varied from 55 to 70 volumes per cent, in those exhibiting toxic symptoms it varied from 65 to 117.

Albumin 1 was in the urine of six patients on the date of examination, pus 2 was found in two specimens. In the second week, albumin 2 was found in six specimens and albumin 1 in five. Four specimens contained casts, eight, pus 1, and one, blood. In the third week, five specimens contained albumin 1, six, albumin 2, and one, albumin 3. Two contained casts and three erythrocytes, four contained pus 1. Albumin and casts were found at some time during the course of treatment in all of the sixteen patients of Group 3.

This is in striking contrast with findings in Group 1 (sixteen milk control patients), one had albumin 1 in the urine and two had albumin 2 at the first examination. At the end of the first week, two had albumin 1 and three had albumin 2 and, at the end of the third week, two had albumin 1 and three had albumin 2. At the first examination, one had casts and eight had occasional pus cells, one week later, one had casts and two had occasional pus cells, in the third week, one had casts and two had occasional pus cells. The blood was normal (Figs 1 and 2).

Of the sixteen patients of Group 2, six had albumin 1 in the urine and five pus 1 at the first examination. In the second week, three had albumin 1, four, albumin 2, and two, occasional pus cells. In the third week two had albumin 1, three, albumin 2, and two, occasional pus cells. Casts were not found during the course of treatment.

The gastric acidity was not controlled in any of the cases of Group 3, as a rule, it was high. The average total acidity during the period of toxemia was 78 and the free hydrochloric acid was 48. The blood pressure remained normal in all except two cases in which it rose from 125 to 150 and from 140 to 160 systolic.

Case 1 is typical of three cases of Group 3. The toxic manifestations, laboratory data, and pathologic findings in this case led us to the supposition that the alkaline treatment may precipitate definite toxic symptoms in patients with renal disease. This was further substantiated by the behavior of two other patients of Group 3, the urine of one (Case 2) appeared normal at examination, after a short period of treatment, the patient showed toxic manifestations, the blood urea rose

to 296 mg for each 100 c c, the creatinin to 5, and casts and albumin appeared in the urine. The alkaline therapy had to be abandoned finally and a posterior gastro-enterostomy was performed for the relief of the gastric symptoms. The patient was last heard from in April, 1921, and is apparently quite well. In the other case, renal function was very low, the right kidney was apparently not functioning because of tuberculosis and there was definite pyelitis in the left kidney. The patient was considered a poor risk for surgery and, since he could not tolerate the usual amount of alkali, he was placed on a soft diet including vegetable purées and cooked fruits, with a small amount of alkali. According to the last report, he had no gastric symptoms.

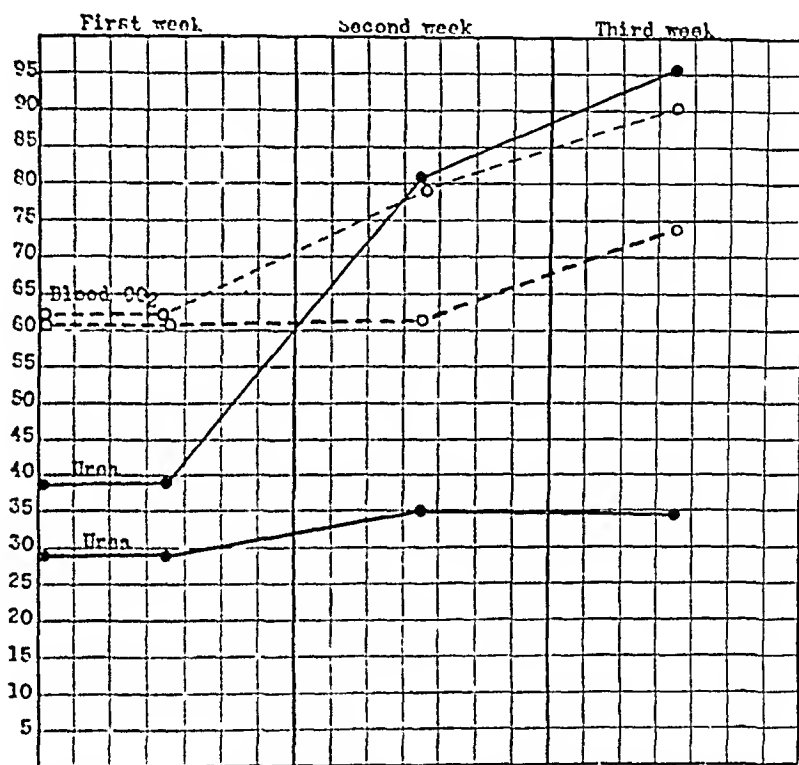


Fig 1—Alkaline reserve and blood urea in toxic and nontoxic cases. Light lines, average of sixteen patients who showed toxic symptoms, and heavy lines, average of sixteen patients who did not show toxic symptoms.

In these three cases at least, we are undoubtedly dealing with marked pathologic condition of the kidneys. In all three cases, the gastric acidity remained persistently high. The average free hydrochloric acid was 62, the average total acids, 102. The point is emphasized that alkaline therapy directed toward the complete neutralization of gastric acidity is not only out of the question, but also harmful.

Cases 3, 4, 5 and 6 are typical of thirteen cases of Group 3, in which there was no clinical or laboratory evidence of nephritis or nephrosis at the onset of treatment. Symptoms of varying degrees of toxemia associated with renal involvement became manifest within

a few days to a few weeks after treatment was instituted. One can hardly be justified in assuming that these patients had definite nephritis at the onset, but rather that renal disease with toxic manifestations was the result of the alkaline therapy. These patients daily received 70 grains of sodium bicarbonate, 56 grains of heavy calcined magnesium, and 105 grains each of calcium carbonate and bismuth subcarbonate. Because of the persistently high acidity, from 70 to 210 grains of calcium carbonate was given daily in hourly dosages of from 5 to 15 grains. We have not definitely determined which one of the salts or metals is responsible for the toxemia. Bismuth subcarbonate was not administered to two patients who developed symptoms of toxemia. All alkalis were temporarily withheld from a third patient

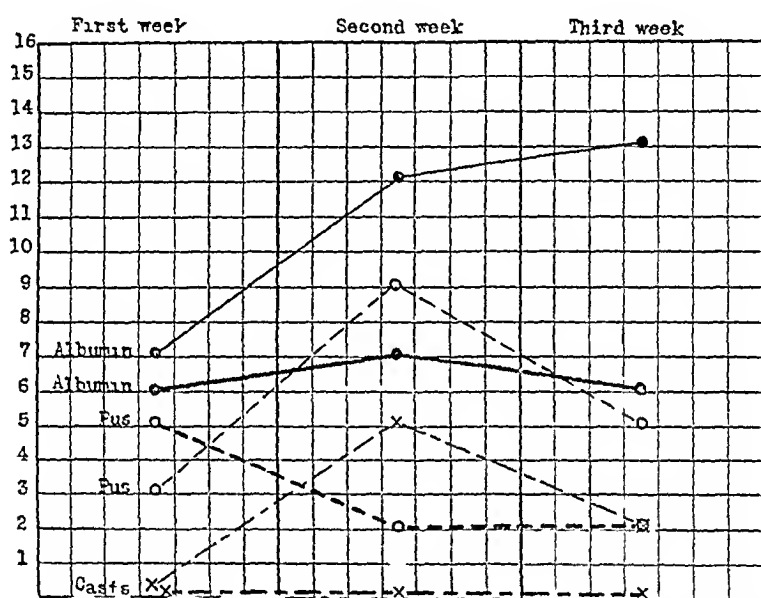


Fig 2—Albumin, pus, and casts in the urine in toxic and nontoxic cases. Light lines, average of sixteen patients who showed toxic symptoms, and heavy lines, average of sixteen patients who did not show toxic symptoms.

who became toxic while taking the usual combination of powders, but because of the resulting epigastric pain, three times the usual amount of sodium bicarbonate was given, without the recurrence of toxic symptoms. Recent unpublished experiments in the clinic indicate that the calcium ion is not the offender. From these facts we are more inclined to regard the nonmetallic ions as being the cause of the toxicity, and perhaps to some extent the combination of heavy metals rather than any specific one. The diet is not the cause, as none of the patients on the diet alone showed toxic symptoms.

The fact that in these cases the acids are persistently high brings up the question of variation in absorption or perhaps depletion of blood chlorid. It is highly conceivable that a condition simulating that pro-

duced mechanically by MacCallum is being produced by chemical means. These patients and patients with gastric tetany have similar blood findings with the exception that in the latter there is a depletion of chlorids in the blood. In the one instance in which a determination of the blood chlorid was made during a period of toxemia it was normal. It is not improbable that these cases are potentially gastric tetany, however, laboratory data as yet do not justify such a conclusion.

The problem of whether or not true alkalosis is produced by the large amounts of alkalis given is yet to be solved. The hydrogen ion concentration was not determined in this study, although on the basis of the high carbon dioxide combining power of the plasma and the administration of large quantities of alkalis we feel justified in applying the term alkalosis to the condition in this group of cases.

### CONCLUSIONS

1. Patients with duodenal ulcer treated by the Sippy method may develop definite symptoms of toxemia associated with renal changes, increased blood urea, and normal or increased carbon dioxide combining power of the plasma. The gastric acidity during the period of toxemia is usually normal or there is hyperacidity.

2. Patients with duodenal ulcer and renal complications are more inclined to develop these toxic manifestations and to a much greater degree.

### REPORT OF CASES

CASE 1 (1348815)—Mr. I. D., aged 66 years, was examined in the Clinic, Feb. 8, 1921. The patient complained of indigestion of fifteen years' duration.

*Previous History*—He had had rheumatism and diphtheria. Attacks of gas on the stomach for from two to three hours after meals, relieved by soda or vomiting had occurred every month or two. For the last five years the attacks had been more severe and prolonged. In August, 1920, he had vomited dark coffee-ground material every few hours for three days. Toward the end of the attack clotted blood and mucus appeared in the vomitus. The stools had been tarry. In November, he had had a similar attack of three days' duration. He had been severely constipated. He had had one tender spot to the right of the middle line half way between the ensiform cartilage and the umbilicus and another 5 cm. below and 5 cm. to the left of the umbilicus. Recently he had felt considerable pain across the middle lumbar region. He had been on a milk diet.

*Examination*—The patient was pale, he had pyorrhea, arteriosclerosis, ankylosis of the left wrist, and double inguinal hernia. There was no tenderness in the abdomen. The systolic blood pressure was 140, the diastolic 75, the pulse was 92 and the temperature 97, hemoglobin was 48 per cent, the erythrocytes numbered 3,080,000 and the leukocytes 6,200. The specific gravity of the urine was 1.013, the reaction acid, there were a few pus cells. Roentgen-ray examination showed a duodenal ulcer and retention Grade 2. The patient weighed 168 pounds. The diagnosis was duodenal ulcer and secondary anemia. February 9, the patient was sent to the hospital for treatment.

*Course*—The patient was put on the alkaline treatment and was free from untoward symptoms for fifteen days. February 26, he became stuporous.

Gastric analysis showed total acids 116 and free hydrochloric acid 100. A second analysis, February 27, showed total acids 70 and free hydrochloric acid 42. March 2, the patient's general condition was much worse. The blood urea was 134 for each 100 cc and creatinin 4.3. The carbon dioxide combining power of the plasma was 100 volumes per cent. There was slight tetany in the arms and hyperstatic congestion in the lungs. The systolic blood pressure was 160, the diastolic pressure was 60. March 3, the condition was similar. March 5, the blood urea had increased to 212, creatinin to 4.2 and the carbon dioxide combining power of the plasma to 112. March 7, the patient's condition was worse and, March 12, he died.

*Necropsy Report*—At necropsy duodenal ulcer and subacute nephritis associated with bilateral bronchopneumonia, tumor of the spleen, moderate prostatic hypertrophy, dental sepsis, and generalized arteriosclerosis were found. Some of the blood vessels of the kidney were sclerosed and there was interstitial, focal, and diffuse lymphocytic infiltration. The glomeruli varied greatly in size. Some had lost their normal structure, while others were completely sclerosed. Most of the capsules were thicker than normal. Most of the alveolar lumina of the lungs were filled with an exudate of erythrocytes, serum, and desquamated epithelial cells. The bronchi were filled with purulent exudate. There was slight hypertrophy of the muscle fibers of the heart. The liver was characterized by a marked increase in intralobular tissue and vacuolated hepatic cells. The normal pancreatic tissue was largely replaced by interlobular tissue. The suprarenal capsule was somewhat thickened.

CASE 2 (A373290)—Mr. G. W., aged 38 years, came to the Clinic, Sept. 26, 1921, complaining of indigestion of three years' duration.

*Previous History*—Attacks of indigestion, which came on two to three hours after meals, were relieved by soda or food. Following a year of freedom from symptoms the patient had a recurrence seven weeks before examination. This attack began with vomiting following a heavy meal and he had since vomited occasionally. Pain, which was localized in the epigastrium, had invariably been relieved by vomiting, or by taking a glass of milk or sodium bicarbonate. The patient lost about 26 pounds in eight weeks, at the time of examination he weighed 156 pounds.

*Examination*—The skin of the patient's face showed smallpox marks, and three areas of lupus erythematosus were noted on the cheeks and lip. The teeth and tonsils were septic. The epigastrium was tender to touch. There were large external hemorrhoids. The blood pressure was 130 systolic and 90 diastolic. The pulse was 96, and the temperature 99 F. The specific gravity of a twelve-hour specimen of urine was 1.020, the reaction acid. Blood urea was 246 mg. A diagnosis of duodenal ulcer was made.

*Course*—Oct. 3, 1921, the patient was placed on medical treatment. At midnight he had pain in the epigastrium, milk tasted sour at this time. October 5, he felt well. The following day he complained of epigastric pain, and more or less nausea, vomiting, and headache until October 28. Symptoms were invariably precipitated by an attempt to neutralize the gastric acidity by the usual Sippy treatment. Forcing alkalis three times led to extreme nausea, vomiting, and prostration. Blood urea on two occasions was 168 and 296 mg. A twelve-hour specimen of urine had a specific gravity of 1.012, acid reaction, albumin 2, and hyaline and granular casts 1.

A posterior gastro-enterostomy under local anesthesia revealed a calloused ulcer of the duodenum about 15 cm. below the pylorus, this had caused moderate obstruction. Convalescence was uneventful. Blood urea dropped to 84 mg.

CASE 3 (A383699)—Mr. H. C., aged 26 years, was examined in the Clinic, Feb. 8, 1922.

*Previous History*—In August, 1918, he began to have dull aching pains in the epigastrium from two to three hours after meals, the pain was relieved

by food, alkalis and belching. He had had persistent diarrhea for one year, and occasional headaches for the last few months associated with dizziness, tinnitus and pain in the scrotum.

*Examination*—The patient weighed 162 pounds. His skin was dry and rough. He had marked dental sepsis. The right lobe of the thyroid was slightly enlarged. There was tenderness on pressure above the umbilicus. The systolic blood pressure was 128, the diastolic was 80, the pulse was 80 and the temperature 98.6 F. The specific gravity of a twelve-hour specimen of urine was 1.027 and the reaction acid. Microscopic examination of the urine was negative. The hemoglobin was 73 per cent, the leukocytes numbered 5,400. Gastric analysis revealed total acids 78 and free hydrochloric acid 58. Roentgen-ray examination of the teeth showed a slight periapical infection, and of the stomach, duodenal ulcer.

*Course*—Feb. 10, 1922, the patient was admitted to the hospital for treatment of the ulcer. After fifteen days of the Sippy treatment he was given an additional 5 grains of calcium carbonate hourly, whereupon he began to have headaches and was nauseated. February 26, gastric analysis revealed total acids 84, and free hydrochloric acid 60. February 27, a distaste for milk was manifested. Examination of a single specimen of urine showed specific gravity 1.011, reaction acid, albumin 1, and occasional erythrocytes and pus cells. February 28, he was slightly dizzy, gastric analysis showed total acids 60 and free hydrochloric acid 20. Blood urea was 38 mg. for each 100 cc. and blood chlorids 600. Carbon dioxide combining power of the plasma was 83 volumes per cent and phenolsulphonephthalein return 35 per cent. March 1, severe occipital headache with nausea and vomiting and profuse perspiration came on. The pain in the epigastrium was slight, the patient appeared drowsy. Alkaline treatment was discontinued, the stomach lavaged, and two-hour feedings of orange juice, cereals, and meat broths were given. At this time the blood urea was 62 mg. for each 100 cc. blood chlorid 630, and the carbon dioxide combining power of the plasma 78 volumes per cent. The specific gravity of the urine was 1.013 and the reaction alkaline, it contained albumin 2, hyaline and granular casts and a few pus cells. March 2 the patient felt much better. The specific gravity of the urine was 1.015, and the reaction acid, it contained albumin 1 but neither casts nor pus cells. March 8, the patient was completely relieved of symptoms, although the acidity of the gastric contents was high, the total acids 118 and free hydrochloric acid 106. The patient was dismissed from observation.

*CASE 4 (A354758)*—Mr. M. R. T., aged 41 years, came to the Clinic, April 7, 1921, complaining of pain in the epigastrium. In 1910, he had had gonorrhea.

*Previous History*—For the last five years, intermittent attacks of pain, occurring one to two hours after meals and localized about 4 cm. above the umbilicus, had been relieved by food or sodium bicarbonate.

*Examination*—The patient appeared well developed and weighed 138 pounds. The blood pressure was 120 systolic and 80 diastolic, the pulse was 76. The hemoglobin was 80 per cent and the leukocytes numbered 13,400. A Wassermann reaction on the blood was negative. The tonsils, which were septic, were removed April 14. A twelve-hour specimen of urine showed specific gravity 1.029, reaction acid, and an occasional pus cell. The blood urea was 34 mg. and the carbon dioxide combining power of the plasma was 65 volumes per cent. Gastric analysis revealed total acids 54 and free hydrochloric acid 44. The roentgen ray revealed duodenal ulcer.

*Course*—Medical treatment was instituted May 1, and the patient remained free from symptoms for one week. May 9, he complained of nausea and vertigo, and two days later he vomited. He said he could not tolerate milk. May 13, additional alkalis were given, as the acids had not been controlled. The nausea and vomiting continued until May 16, when treatment was temporarily stopped and frequent small feedings were given. During the period



of toxic symptoms free hydrochloric acid varied from 20 to 32, the blood urea rose from 40 to 70 mg and the carbon dioxide combining power of the blood plasma was 70 volumes per cent. Examination of the urine showed specific gravity 1.009, reaction alkaline, and albumin 1.

CASE 5 (A357910)—Miss M. H., aged 25 years, came to the Clinic, May 12, 1921, complaining of attacks of indigestion of two years' duration.

*Previous History*—For intervals of one to three months she was well. The attacks, which terminated in vomiting, were accompanied by pain and soreness in the epigastrium, sour stomach, and heartburn. Occurrence of the distress bore no relation to feeding.

*Examination*—The patient weighed 111 pounds and was 5 feet, 4 inches tall. The blood pressure was 120 systolic and 80 diastolic, the pulse was 72. Hemoglobin was 73 per cent and the leukocytes numbered 5,900. Examination of a twelve-hour specimen of urine showed specific gravity 1.029, reaction acid, and an occasional pus cell. Gastric analysis revealed total acids 88 and free hydrochloric acid 50. A lesion at the outlet of the stomach was demonstrated by the roentgen ray, and a diagnosis was made of pyloric ulcer.

*Course*—May 18, the patient was placed on Sippy treatment and remained free from symptoms for two weeks. June 1, she complained of nausea and slight headache, and in the evening she vomited. Gastric analysis showed total acids 18 and free hydrochloric acid 0. Blood urea was 64 mg. The urine had a specific gravity of 1.006, reaction alkaline, and albumin 1. Alkalis were discontinued for one day, the symptoms cleared up and did not return when the treatment was resumed.

CASE 6 (A355435)—Mr. A. B., aged 24 years, came to the Clinic, April 15, 1921, complaining of a gnawing pain in the epigastrium.

*Previous History*—An appendectomy had been performed in 1919. Since December, 1920, he had had two attacks of epigastric pain coming on two hours after meals, and readily relieved by a glass of milk.

*Examination*—The patient appeared well developed and weighed 140 pounds. A definite area of tenderness was present in the epigastrium. The blood pressure was 115 systolic and 70 diastolic, the pulse 84. The tonsils were septic. Examination of a twelve-hour specimen of urine (500 cc) showed specific gravity 1.032, reaction acid, and an occasional pus cell. The blood urea was 28 mg and the carbon dioxide combining power of the blood was 68 volumes per cent. Total acids were 32, and free acids 22. A diagnosis of duodenal ulcer was confirmed by the roentgen ray.

*Course*—Medical treatment was instituted April 18, and the patient remained free from symptoms for seventeen days. May 4, he complained of dizziness and nausea, and later he vomited. The specific gravity of the urine was 1.011 and reaction acid, there was albumin 2 with casts 1. The blood urea was 84 mg and the carbon dioxide combining power of the plasma 84 volumes per cent. Nausea and dizziness subsided within two days when alkalis were discontinued and six daily feedings of milk toast, vegetable purees, and custards were given. May 10, treatment was resumed and the patient had no further symptoms.

# A SIMPLE IMMERSION ELECTRODE FOR TAKING CLINICAL ELECTROCARDIOGRAMS

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Because of its simplicity and ease of operation, and because it has certain technical advantages, I wish to describe an electrode for use when taking electrocardiograms of ambulatory patients. Electrodes consisting of a metal plate bound to the extremity by bandages wet with hot salt solution are commonly used for bed patients,<sup>1</sup> but for ambulatory patients the zinc—zinc sulphate—salt solution type of non-polarizable electrodes are recommended.<sup>2</sup> These latter are a quite unnecessary complication of the technic. The simple electrode to be described will take technically perfect records.

It consists of a glass tank for each extremity, that for the arms being a cylinder about 7 x 10 inches and that for the leg being rectangular, about 7 x 7 x 12 inches (a fish aquarium). In these are stood metal plates 4 inches wide and extending up above the top of the tank, to which plates the wires from the galvanometer are attached. Plates of lead have the advantage of being least corrosive but any metal would do.

Into each tank is poured a concentrated solution of sodium chlorid (from 10 to 20 per cent) to the depth of about three inches. This should be heated before being placed in the tank to about as high a temperature as can be borne without discomfort by the skin of the hand, for this will help to ensure a low resistance of the patient's skin to the electric current, probably by dilating the capillaries.

The patient sits erect or is semi-recumbent in a comfortable chair and places each hand and the left foot in the solution of the appropriate tank. He must be comfortable, and more or less relaxed physically in order to avoid the fine movements of the string which arise from the activity of the voluntary muscles. Physical relaxation demands that the patient shall not have to hold the elbows to keep from pressing his knuckles heavily against the bottom of the tank, or to hold the fingers extended to reach down into the salt solution, so provision must be made for raising or lowering the level of the tanks for the hands. Placing them on a screw top stool is fairly satisfactory, or on a pile of wooden blocks each 1½ inches thick.

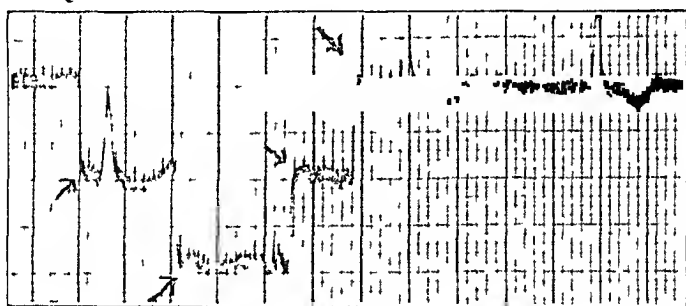
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1 James, W B, and Williams, H B. The Electrocardiogram in Clinical Medicine, Am J M Sc **140** 408, 1910

2 Lewis, T. Mechanism and Graphic Registration of the Heart Beat, London, 1920

The patient's skin should not come in contact with the metal plate for this will cause a large current in the galvanometer circuit which must be compensated for by the operator. These electrodes do not introduce an error due to polarization, although they are, technically, polarizable electrodes. The surfaces in contact with the solution are so infinitely large in proportion to the electric currents encountered that the error due to polarization is reduced to less than a detectable amount. The situation is the same as has been shown to be the case for the bandage electrodes.<sup>3</sup>

There is one other feature about these electrodes which is a great point in their favor. The overshooting which comes from a high resistance of the patient's skin to the passage of the electric current is a much less frequent occurrence than when bandage electrodes are used. The resistance tends to be lower, possibly because of the different



The vertical lines measure off time intervals. Between each line is 0.04 second and between each accentuated line is 0.20 second (one fifth). Horizontal lines measure the strength of the electricity. Each of the series of steps is due to a difference of 1 millivolt (0.001 volt) introduced in the circuit and is seen to be very close to 1 cm. Each of the horizontal lines is 1 mm apart. A deflection of 1 cm then equals 1 millivolt.

character of the skin of the hands and the forearms, the foot and the leg, and even with the same resistance, the overshooting is less. I am unable to offer an explanation of this but it is a common observation. The resistance may be as high as 6,000 ohms and yet the overshooting is negligible, whereas with large German silver plates and bandages the overshooting may be great with only 2,500 ohms resistance.

The accompanying illustration is an electrocardiogram taken by Lead II, with these electrodes, the upward and downward stepping of the base line being caused by the operator turning in and out of the circuit containing patient and galvanometer potential differences of 1

<sup>3</sup> Pardee, H. E. B. An Error in the Electrocardiogram Arising in the Application of the Electrodes, *Arch Int Med* **20** 161 (Aug.) 1917. Cohn, A. E. A New Electrode for Use in Clinical Electrocardiography, *Arch Int Med* **26** 105 (July) 1920.

millivolt It will be seen that the steps show no sign of overshooting, giving a clear sharp ending at almost as near a right angle as at their beginning When the control curve shows this sharp angled ending without overshooting we know that polarization is not present, that the record is free from any error from this source, and likewise that the skin resistance is low

# PAROXYSMAL VENTRICULAR TACHYCARDIA

REPORT OF ONE CASE WITH NORMAL TYPE OF AURICULAR MECHANISM AND THREE WITH AURICULAR FIBRILLATION \*

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Paroxysmal tachycardia of ventricular origin is one of the rarest disturbances of the cardiac mechanism. The first case with electrocardiographic tracings was recorded by Lewis<sup>1</sup> in 1909. Robinson and Herrmann<sup>2</sup> recently reported four cases and discussed the criteria on which they consider a diagnosis justifiable. The points emphasized by these authors may be stated briefly as follows:

1. Electrocardiograms are necessary to differentiate ventricular tachycardias from those of auricular origin.

2. The condition is most clearly shown when a succession of auricular complexes can be made out occurring independently of and at a slower rate than the complexes of ventricular origin.

3. The ventricular complexes are distinctly abnormal in form, but this alone cannot be taken as absolute proof that the impulses are of ventricular origin, as changes in form may be caused by disturbances in intraventricular conduction.

4. The presence of isolated ectopic ventricular beats before or after a paroxysm is regarded as evidence in favor of the tachycardia being of ventricular origin, especially when the form of the complexes of the isolated beats is the same as the form of the paroxysm.

Lewis<sup>3</sup> has pointed out that in certain cases, tracings showing the beginnings of paroxysms are of great value in determining the origin of the abnormal beats. He states that several of the cases published are clear instances of paroxysms arising in the ventricles and are unmistakable because the first beat of the paroxysm has the same relations to the preceding normal rhythm as has a ventricular extrasystole.

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\* From the William Pepper Clinical Laboratory, University of Pennsylvania and the Division of Cardiology of the Laboratory of the Philadelphia General Hospital.

1. Lewis, T. Single and Successive Extrasystoles, *Lancet* 1:384 (Feb. 6) 1909.

2. Robinson, G. C., and Herrmann, G. R. Paroxysmal Tachycardia of Ventricular Origin and Its Relation to Coronary Occlusion, *Heart* 8:59 (Feb.) 1921.

3. Lewis, T. The Mechanism and Graphic Registration of the Heart Beat, London, 1920.

Robinson and Heilmann, reviewing the cases previously reported, accept six as undoubted instances of ventricular tachycardia. These are the two cases of Lewis,<sup>4</sup> and one each of Hart,<sup>5</sup> Butterfield and Hunt,<sup>6</sup> Vaughn,<sup>7</sup> and Willius.<sup>8</sup> Cohn's case<sup>9</sup> is also an undoubted instance of the condition. Since Robinson and Heilmann's paper, three clear cases have been published by Gallavardin,<sup>10</sup> two by Singer and Winterberg,<sup>11</sup> one by Marvin and White<sup>12</sup> and one by Dieuaide and Davidson.<sup>13</sup> Singer and Winterberg designate the abnormal mechanism in one of their cases as extrasystolic arrhythmia bordering on paroxysmal tachycardia, but some of the periods of rapid rhythm, they state, persisted for at least 60 successive beats. The case should, therefore, be classed as one of paroxysmal tachycardia. The tracing of Dieuaide and Davidson's patient, taken five hours before death, shows an abrupt transition during complete heart block from a typical slow ventricular rate and complexes of supraventricular type to a rapid regular rhythm of ventricular origin. Bishop<sup>14</sup> has recently published tracings of a case (Case 1) in which the form of the ventricular complexes suggests that the beat is arising in a ventricle, but no other evidence in favor of that view is offered. A ventricular origin of the abnormal rhythm is also suggested by the form of the ventricular complexes in the tracings published by Barcroft, Bock and Roughton<sup>15</sup> in connection with the report of their studies of respiration and blood flow during paroxysmal tachycardia.

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4 Lewis, T. The Mechanism of the Heart Beat, London, 1911.

5 Hart, T. S. Paroxysmal Tachycardia, *Heart* **4** 128 (Nov. 30) 1912.

6 Butterfield, H. G., and Hunt, G. H. Observations on Paroxysmal Tachycardia, *Quart. J. M.* **7** 209 (April) 1914.

7 Vaughn, W. T. A Study of Paroxysmal Tachycardia with Especial Reference to Tachycardia of Ventricular Origin, *Arch. Int. Med.* **21** 381 (March) 1918.

8 Willius, F. A. Paroxysmal Tachycardia of Ventricular Origin, *Boston M. & S. J.* **178** 40 (Jan. 10) 1918.

9 Cohn, A. E. The Present Status of the Electrocardiographic Method in Clinical Medicine, *Am. J. M. Sc.* **151** 529 (April) 1916.

10 Gallavardin, L. Tachycardie Paroxystique Ventriculaire, *Arch. d. mal. du coeur* **13** 121 (March) 1920. Tachycardie Ventriculaire Terminale, *Arch. d. mal. du coeur* **13** 207, 210 (May) 1920.

11 Singer, R., and Winterberg, H. Chinin als Herz- und Gefassmittel, *Wien. Arch. f. inn. Med.* **3** 329 (Nov. 15) 1921.

12 Marvin, H. M., and White, P. D. Observations on Paroxysms of Tachycardia, *Arch. Int. Med.* **29** 403 (April) 1922.

13 Dieuaide, F. R., and Davidson, E. C. Terminal Cardiac Arrhythmias, *Arch. Int. Med.* **28** 633 (Nov.) 1921.

14 Bishop, L. F. Early Signs of Fibrillation of Ventricle as Shown by Occurrence in Electrocardiogram of Periods of Ventricular Tachycardia, *Ann. Med.* **1** 58 (April) 1920.

15 Barcroft, J., Bock, A. V., and Roughton, F. J., Observations on the Circulation and Respiration in a Case of Paroxysmal Tachycardia, *Heart* **9** 7 (Dec. 14) 1921.

In the cases thus far reported, four types of auricular mechanism in association with the tachycardia have been recognized. These are (1) the normal type of auricular action in which the auricles are beating independently of and at a slower rate than the ventricles, (2) retrograde auricular beats due to the stimulation of the auricles from the ventricles, (3) auricular flutter and (4) auricular fibrillation. In some tracings, no waves due to auricular activity can be identified.

The combination of auricular flutter or fibrillation with paroxysmal ventricular tachycardia is extremely rare (except when the latter is caused by drugs), only one case of each having been reported, both by Gallavardin. Dieuaide and Davidson obtained a series of ectopic ventricular beats during the course of auricular fibrillation in a patient a few minutes before death. While the rate in their case was scarcely rapid enough to be classed as a tachycardia, it would appear that the mechanism was essentially the same as that found in paroxysmal ventricular tachycardia. This view is supported by the fact that brief series of ectopic ventricular beats of infrequent rate were also observed in Gallavardin's case of auricular fibrillation and paroxysmal ventricular tachycardia and in our Case 2 to be described later.

#### REPORT OF CASES

**CASE 1**—M. H., negress, 20, a waitress, was admitted to the medical division of the University Hospital, Jan 22, 1913, complaining of shortness of breath and palpitation of the heart. She stated that she had been "short-winded" as long as she could remember but otherwise had been as well as usual until five days before admission when suddenly, while working, she felt her heart beat, became weak, dizzy and short of breath and had a pain in her head. She also had a smothering sensation when she lay flat. These symptoms continued up to the time of her admission. She thought her abdomen had swollen since she had become ill.

*Previous History*—She gave a history of having had measles, mumps, chickenpox, pneumonia, bronchitis and typhoid but no rheumatism, chorea, tonsillitis or scarlet fever. There was nothing of importance in the social and family history.

*Physical Examination*—The physical examination on admission showed slight cyanosis but no respiratory distress. Vigorous rapid pulsations in the neck were noted. The heart was definitely enlarged with a transverse measurement of 17 cm. No murmurs were heard. The cardiac rate was 190. Moist râles were heard at the bases of both lungs. The liver extended 4 cm. below the costal margin in the right midclavicular line and there was marked tenderness over it. There was slight pretibial edema.

*Course*—The rapid heart action lasted until fourteen hours after admission when the rate dropped to 82. During the next few days there were numerous extrasystoles and at times a bigeminal pulse. Five days after admission there was another attack of tachycardia, which lasted sixteen and one-half hours, and two days later a third attack, lasting five hours. During the remainder of her stay in the hospital, a period of three weeks, there were no further attacks but extrasystoles were constantly noted. At the time of her discharge, she felt quite as well as she had before the onset of her illness.

*Laboratory Examination*—Examinations of the blood and urine showed nothing of importance. The Wassermann reaction was negative.

Electrocardiograms were made by Dr Thomas Cope both during the periods of tachycardia and in the intervals. A tracing made during a period of tachycardia (Fig 1) shows ventricular complexes of a distinctly abnormal type. In Lead 2, waves due to the auricular activity can be made out and it is seen that the auricular contractions are occurring independently of and at a slower rate than the ventricular. In Figure 2, made during a period of slower heart action, is shown the supraventricular type of ventricular complexes. There are present a number of extrasystoles mostly auricular in origin. None of the ventricular complexes are similar to those found during the period of tachycardia.

CASE 2—W. N., a white male, aged 61, was admitted to the Philadelphia General Hospital Feb 1, 1922, showing the signs of some grave disturbance of the circulation. The breathing was Cheyne-Stokes in type.

*Precious History*—The patient was dull, stuporous and quite irrational, and for this reason a precise history could not be obtained. However, it appeared that he had been breathless on rather moderate exertion for at least seven years, and at times had had edema. He had been able to continue his work as a motorman until Oct 1, 1921, when he had to give up on account of breathlessness, cough and edema. No information could be obtained as to whether these symptoms had come on suddenly or not. The rest of the history elicited was unimportant except for a questionable attack of rheumatic fever at 25.

*Physical Examination*—On examination, there was found to be extensive edema of the legs including the thighs, and also of the abdominal walls. There were signs of fluid in both pleural spaces, and questionable signs of ascites. The liver was greatly enlarged. The cardiac apex impulse was located in the fifth interspace 4 cm. outside the nipple line and 12.5 cm. from the midclavicular line. No murmurs were heard. On admission, the cardiac rhythm was found to consist of periods of rapid regular action with a rate of 164, followed by periods of irregular rhythm with a rate varying between 48 and 60. The two types of rhythm seemed to share the cardiac action about equally, each lasting usually from one to two minutes. The periods of tachycardia began and terminated abruptly. The pulse was barely perceptible and there was a large pulse deficit.

*Laboratory Examination*—The urine showed signs of renal congestion, there being a cloud of albumin with a moderate number of casts. The specific gravity was 1.024. The blood urea nitrogen was 20 mg. per hundred cubic centimeters. The blood Wassermann was negative.

*Treatment*—At the time of admission, a clinical diagnosis of auricular flutter was made, the periods of slow irregular heart action being attributed to varying degrees of *A-V* block. Accordingly the patient was given 4 c.c. of the tincture of digitalis followed six hours later by a similar dose. An electrocardiogram obtained eight hours after admission showed that the cardiac mechanism was slow auricular fibrillation interrupted by paroxysms of tachycardia with complexes of the ventricular type. The administration of digitalis was discontinued, and as far as could be determined, the medication did not influence the cardiac action in any way. The alternation of rapid regular and slow irregular action persisted as long as the patient lived.

The paroxysms of tachycardia were never of very long duration, the longest one timed being four minutes. As far as could be determined, there was no greater circulatory embarrassment during their presence than during the periods of slow rhythm. The patient was, however, conscious of the rapid beating of his heart. His condition gradually grew worse. Large amounts of fluid were removed from both sides of the chest but without improvement. The mental state became more confused, restraint being required to keep him in bed. February 8, following a violent vomiting spell, sudden death ensued.

*The Electrocardiograms*—Many tracings were made from which have been selected those presented in Figures 3, 4, 5, 6 and 7, to illustrate the types of cardiac action observed. During the periods of slow irregular ventricular activity (Figs 3 and 4) the auricles are observed to be fibrillating. There are



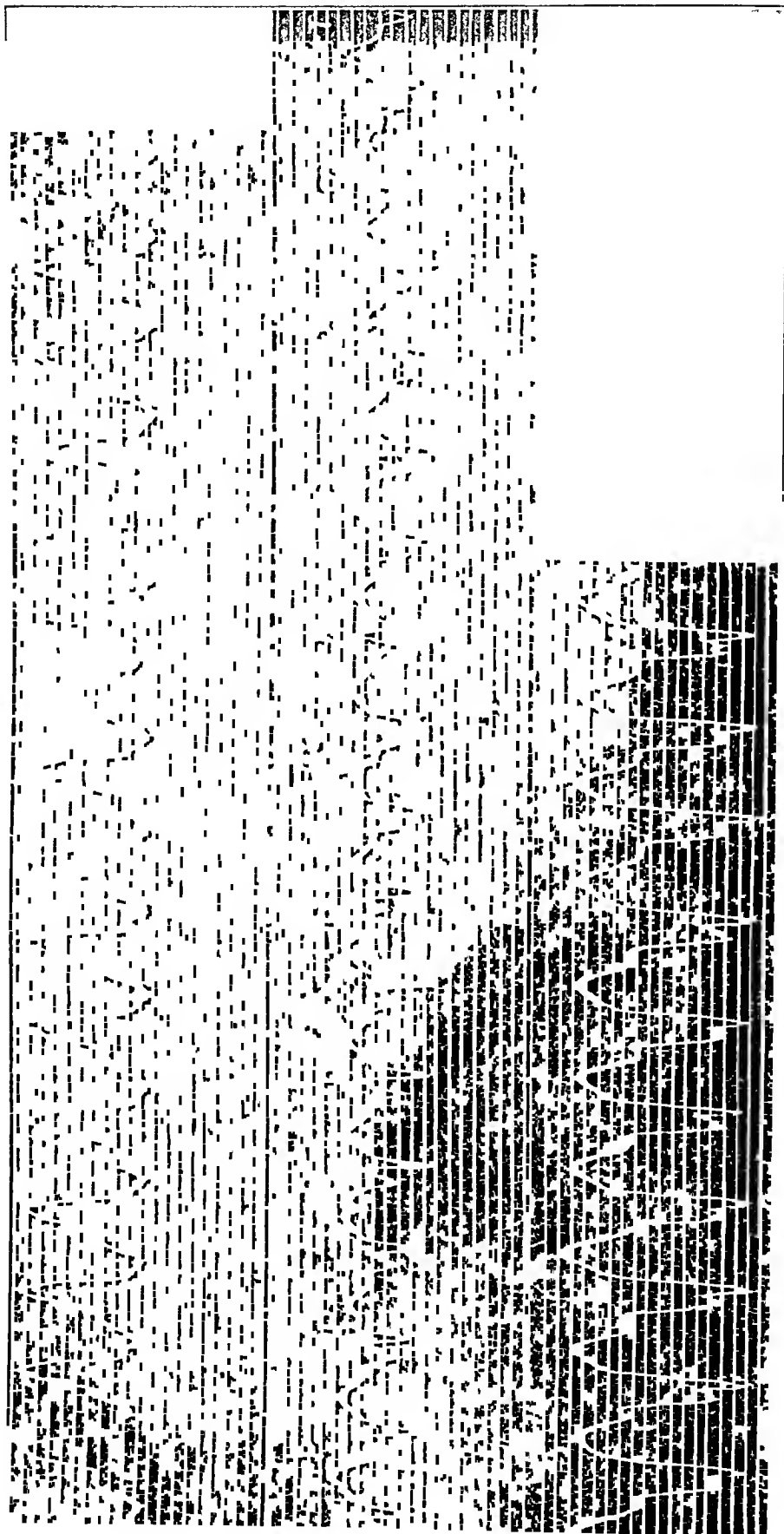


Fig 1—Case 1 Tracing made during a period of tachycardia The evidences of auricular action are distinct in Lead II, but are not discoverable in Leads I or III The auricular rate is 125 and the ventricular rate 192 The photographic paper was not moving evenly Retouched

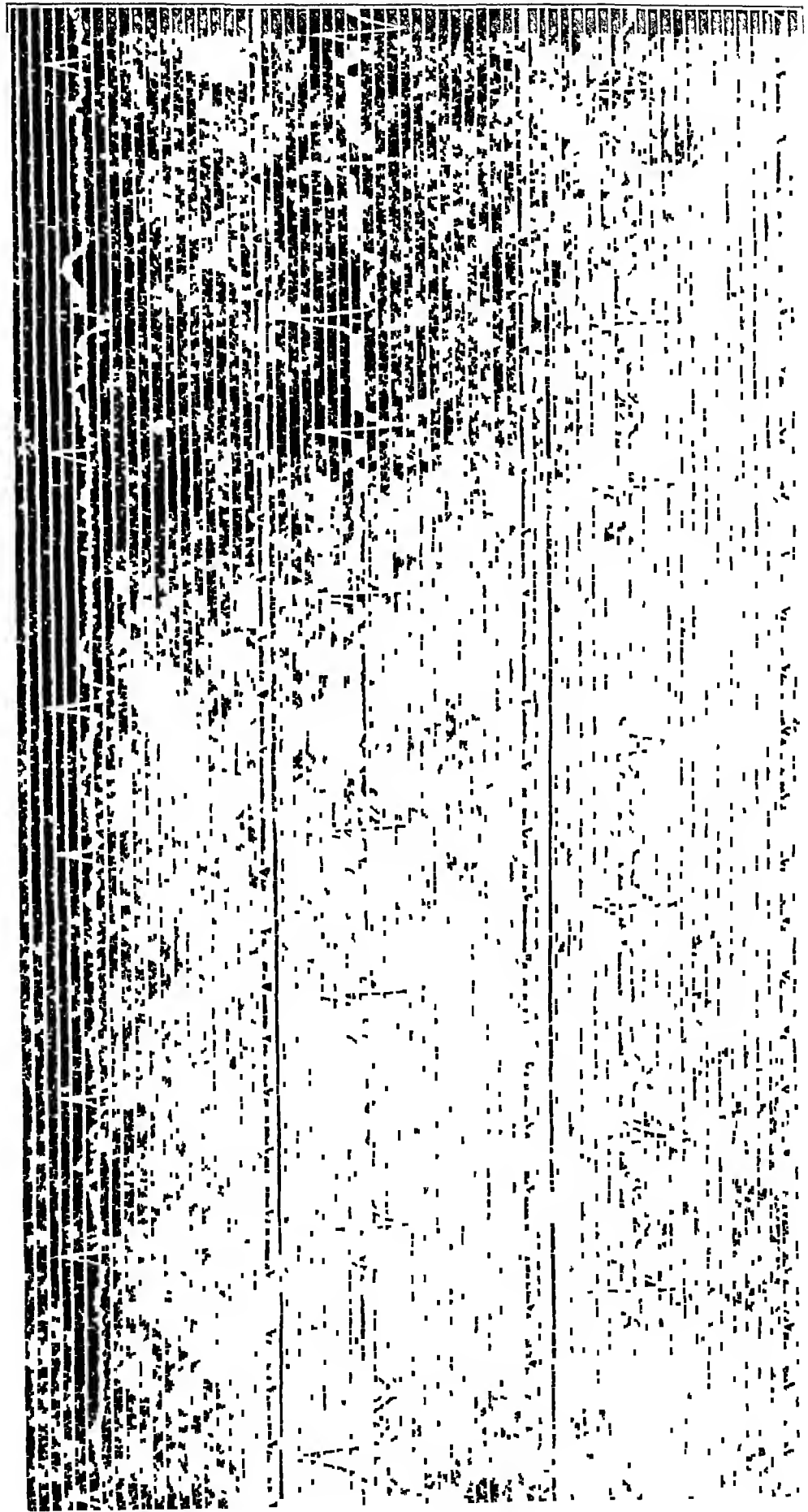


Fig 2—Case 1 Tracing made during an interval between attacks of tachycardia Numerous extrasystoles, mostly of supraventricular type Retouched

numerous complexes of ventricular type, they are more frequent in some tracings than in others but at no time were more than six sequential complexes of supra-ventricular type recorded. In nearly every instance each beat of ventricular type is paired with the preceding beat in such a way that their relations are practically identical with those of the other couples in the same tracing. The time intervals between the first and second beats of the couples do not vary more than 0.01 or 0.02 second in any electrocardiogram, although slightly greater variations are observed in tracings made at different times. Occasionally all the beats were coupled (Fig 5) and gave an element of regularity to the arrhythmia.

During the periods of tachycardia (Figs 4 and 6) all the complexes are of ventricular type and similar in form to the second of the paired beats. Figure 4 shows the onset of paroxysms. In each instance, the relations of the first complex of ventricular type initiating the paroxysm to the preceding supra-ventricular complex are the same as those of paired beats, and the time intervals are the same.

All tracings of the first few beats of paroxysms show slight irregularity of ventricular action. This is more marked in some paroxysms than others and in Figure 6 an extreme instance of this irregularity is seen. In the short paroxysms, the ventricular action was slightly arrhythmic throughout but in the longer ones, it invariably settled down to a perfectly regular rhythm. At the offset, there tended to be slight slowing (Fig 4) which was particularly marked in the last cycle before the resumption of the slow action.

CASE 3—E. J., white, male, aged 18, was admitted to the Medical Division of the University Hospital Sept. 10, 1921, complaining of weakness and swelling of the abdomen and legs. He stated that at the age of 5 he had had an attack of acute articular rheumatism which kept him in bed for several months. He recovered entirely but three years later had an illness in which there was high fever and his heart was affected. After this he was always weak and had palpitation on exertion. From the age of 13, there were periods of cardiac breakdown every year which kept him away from school for a part of the time. The attack which brought him to the hospital was worse than any of the previous ones and instead of improving after rest in bed as he had done before, he gradually lost ground during a period of three months. He was very weak and short of breath and troubled by palpitation. There had been increasing swelling of the legs and abdomen and shortly before admission, of the left arm.

*Physical Examination*—The patient was a fairly well developed boy for his age. He was orthopneic and somewhat cyanotic. There was marked edema of the legs and flanks. The left arm was greatly swollen, but the right appeared normal. There was a small aneurysm of the outer end of the innominate artery.<sup>16</sup> The liver was markedly enlarged and there was moderate ascites. The heart was tremendously enlarged, the area of percussion dulness extending from 6 cm. to the right of the midsternal line to the left midaxilla. There was a short systolic murmur at the apex. The ventricular action appeared to be totally irregular except for occasional runs of regular rhythm lasting a few seconds to nearly a minute. The rate during these periods of regular rhythm was counted a number of times and was always found around 140. During the periods of irregular rhythm, the rate was much slower.

*Laboratory Examination*—The urine showed a cloud of albumin and numerous hyaline, light and dark granular casts. The phenolsulphonephthalein excretion in two hours was 25 per cent, and the blood urea nitrogen 60 mg. per hundred cubic centimeters. The blood count was normal, except for a slight leukocytosis of 12,900. The blood Wassermann was negative.

*Course*—The patient remained in the hospital for ten days, but after the second day, no more of the short runs of regular tachycardia were noted and the ventricular action appeared to be continuously irregular. Digitalis was used freely but apparently without effect. He died ten days after leaving the hospital.

16 To be reported elsewhere

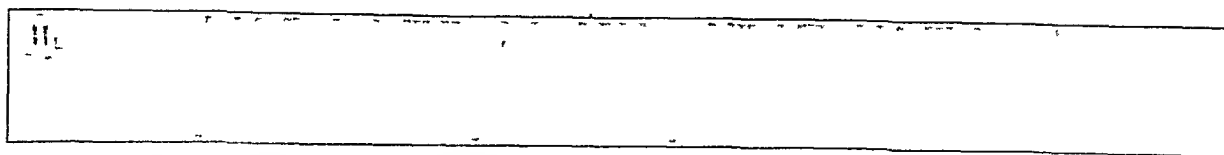


Fig 3—Case 2 Auricular fibrillation, slow ventricular rate and one complex of ventricular type The usual type of cardiac action observed between paroxysms of tachycardia

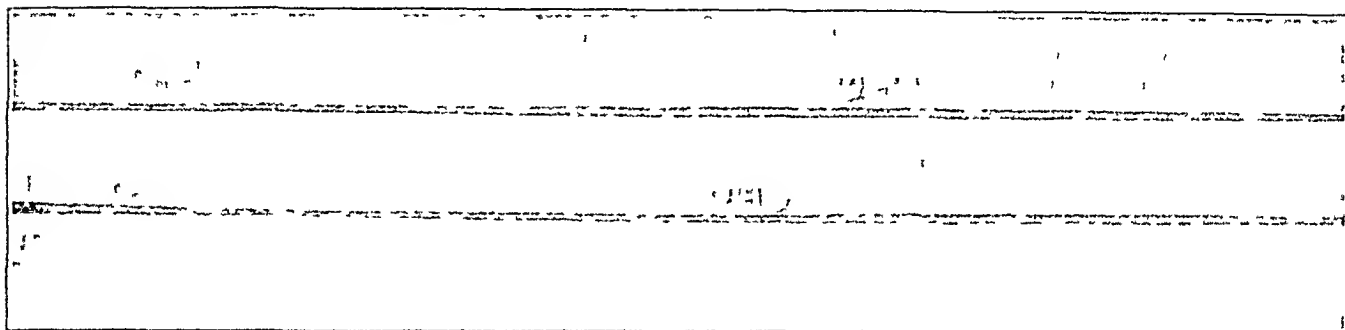


Fig 4—Case 2 Leads I and II show the onsets of paroxysms and Lead III an offset The paroxysms are initiated by two beats identical in their relationships with the isolated coupled beats The rhythm at the beginning of paroxysms is not quite regular There is lengthening of the last cycle before the offset

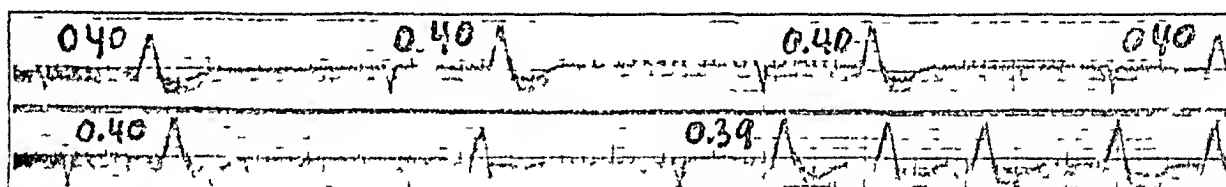


Fig 5—Case 2 Continuous tracing, Lead III Five pairs of coupled beats in succession, an isolated complex of ventricular type and a short paroxysm initiated by a pair of coupled beats The short paroxysm is quite irregular

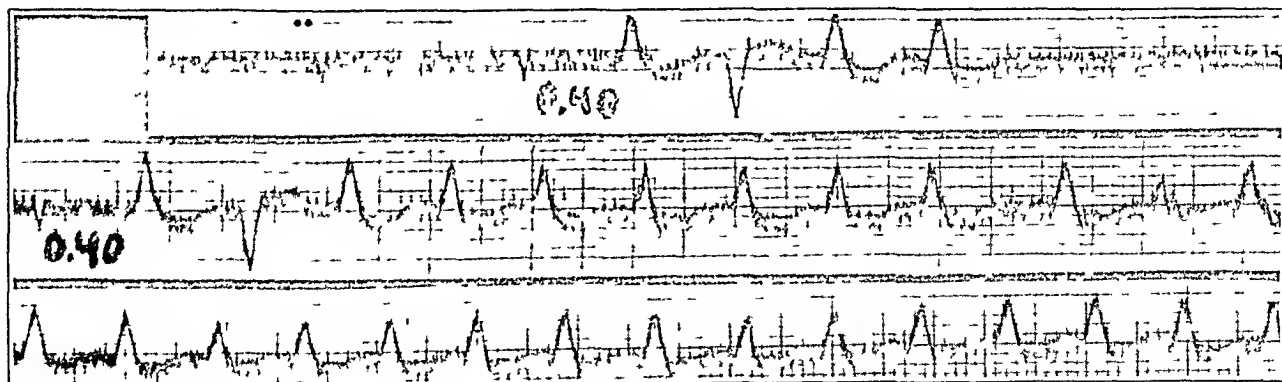


Fig 6—Case 2 Continuous tracing, Lead III Unusual duration of irregularity at the beginning of one of the longer paroxysms

*Clinical Diagnosis*—Chronic rheumatic myocardial disease, cardiac failure, passive congestion, thrombosis of the left axillary vein, aneurysm of the innominate artery, probably mycotic in origin, chronic diffuse nephritis. The clinical diagnosis of the arrhythmia was auricular flutter, the periods of regular rhythm being interpreted as two to one *A-V* block. This view was favored by the fact that, on the day of admission, having the patient sit erect was often followed by short periods of regular tachycardia with a rate always around 140.

*Electrocardiograms*—These showed that the clinical diagnosis of the arrhythmia was incorrect. All the tracings made except one showed auricular fibrillation and occasional complexes of ventricular type. The one unusual tracing (Fig 8) shows the end of a period of rapid regular rhythm with complexes of ventricular type. At the offset of the paroxysm, auricular fibrillation is again evident. The tracing also shows three pairs of coupled beats shortly after the termination of the paroxysm. The time intervals between the first and second of the paired beats were 0.43, 0.42 and 0.43 second, respectively. The form of the complexes of isolated beats of ventricular type, the paroxysm of tachycardia and the second of the paired beats following the paroxysm are all the same. The cardiac rate during the paroxysm was 136, the length of the ventricular cycles being 0.44 second.

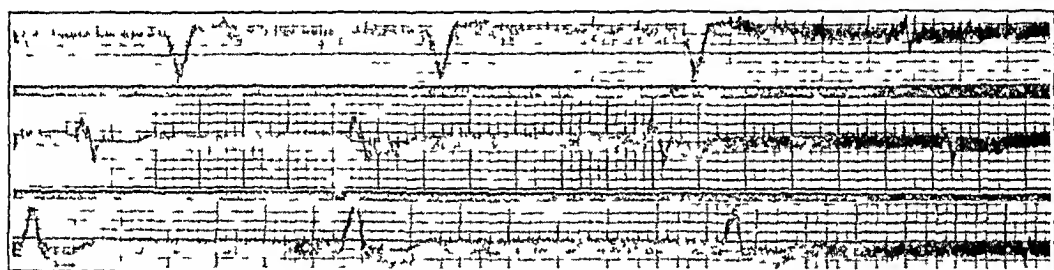


Fig 7—Case 2 Leads I, II and III. Brief periods of successive beats of ventricular type recurring slowly and somewhat irregularly.

**CASE 4**—E. W., a woman, aged 58, was admitted to the medical Division of the University Hospital July 3, 1921, complaining of goiter and swollen legs. She stated that she had first noticed enlargement of the neck about seven years previously and for five or six years had had some difficulty in swallowing. For a few months before admission she had been nervous, suffered from cardiac palpitation, precordial pain and a feeling of oppression and shortness of breath on slight exertion. She had lost 17 pounds in the last ten months before admission.

*Physical Examination*—She was a moderately emaciated woman appearing to be about the age stated. The thyroid gland was enlarged, particularly the right lobe. In the region of the isthmus, there was a mass the size of a walnut and directly above a small mass apparently attached to the larynx. The heart was greatly enlarged and had a transverse measurement of 16 cm. There was a systolic murmur at the apex. The rate was very rapid and the rhythm apparently totally irregular. A few crackling râles were heard at the bases of both lungs, the liver was enlarged and there was moderate swelling of the legs.

*Laboratory Examination*—The blood and urine examinations showed nothing of importance. The metabolic rate was 377 per cent above the normal. The blood Wassermann was strongly positive.

*Clinical Diagnosis*—Syphilis, adenoma of thyroid, chronic myocardial disease, cardiac failure with passive congestion and auricular fibrillation.

An electrocardiogram (Fig 9) confirmed the diagnosis of auricular fibrillation, but showed in addition a paroxysm of six rapidly recurring beats in which the complexes were of ventricular type. An isolated complex of the same type occurred shortly after the paroxysm and the time interval between it and the preceding beat (0.38 second) is equal to that between the first beat of the paroxysm and the beat preceding it. The rhythm, during the paroxysm, was not quite regular.

*Treatment*—The patient received quinidin sulphate and the normal rhythm was restored within two days. While a tracing was being made shortly after the resumption of normal rhythm, a short paroxysm of rapid rate with wide excursions of the string shadow of the galvanometer was observed but could not be recorded. No more paroxysms were observed.

Improvement was rapid following the restoration of normal rhythm, and cardiac compensation was quickly restored. Antisiphilitic treatment was then given. The patient left the hospital after a stay of three weeks, and six months later reported to a social worker that she was well. She refused, however, to return to the hospital for further study.

#### DISCUSSION

In Case 1, the requirements of Robinson and Herrmann for the diagnosis of paroxysmal ventricular tachycardia are satisfied. The ventricular complexes are distinctly abnormal during the paroxysms, their form being that of contractions arising in the left ventricle. The auricular beats are independent of the ventricular and occur at a slower rate. This is the fifth case to be reported in which the waves of independent auricular contractions have been recognized during the paroxysms. The other cases are those of Butterfield and Hunt, Cohn, Robinson and Herrmann, and Gallavardin. In the two cases reported by Lewis in which the paroxysms were very brief, the auricular rhythm did not appear to be disturbed although no auricular waves were discernable during the paroxysms.

*The Recognition of Beats of Ventricular Origin During Auricular Fibrillation*—In the presence of auricular fibrillation, the diagnosis of abnormal ventricular mechanisms such as ventricular extrasystoles or ventricular paroxysmal tachycardia lacks the confirmation that may ordinarily be obtained from an analysis of the auricular action. The origin of a single beat with an abnormal complex during fibrillation may be quite uncertain since temporary intraventricular defect in conduction may cause a beat of supraventricular origin to simulate a ventricular extrasystole. Under certain conditions however, as Lewis<sup>3</sup> has pointed out, the diagnosis of ventricular extrasystoles during fibrillation can be made beyond a reasonable doubt. Such is the case when (1) there is coupling of beats, (2) the first beat of the couple has a complex of supraventricular type and the second of ventricular type and (3) the various paired beats correspond to one another in their relations, including the time interval between the two beats. These conditions are abundantly fulfilled in our Case 2 and the second of the numerous paired beats observed may be regarded beyond reasonable

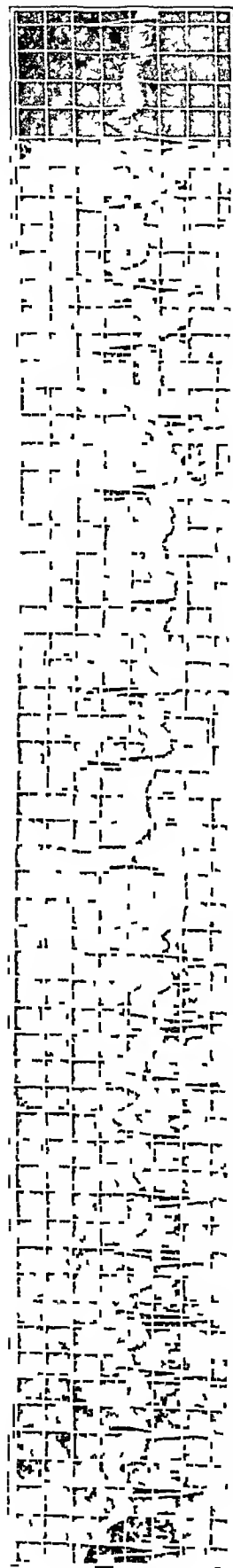


Fig 8—Case 3 End of a paroxysm of tachycardia (Lead I) At the right, three pairs of coupled beats, the second beat of each couple having complex identical in form with those found during the paroxysm The ventricular rate during the paroxysm is 136 Retouched

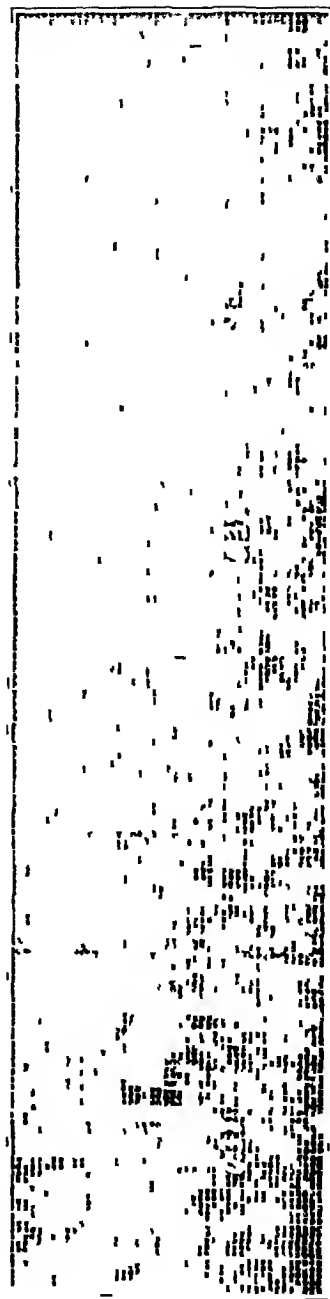


Fig 9—Case 4 Lead III Short paroxysm of beats with complexes of ventricular type The isolated beat of ventricular type is coupled with its preceding beat as is the first beat of the paroxysm A complex of supraventricular type is more premature than the abnormal complexes

doubt as being ventricular. If the tracings showing the beginnings of paroxysms be compared with the coupled beats, it will be observed that each paroxysm is initiated by two beats that are in all respects similar to the isolated couples. Following the second beat, there is found a succession of ventricular complexes having the same form and consequently portraying the same course of the excitation wave. Thus the origin of the paroxysms may also be regarded justifiably as ventricular.

In Case 3, the evidence is similar to that of Case 2, although not quite so complete since no tracing of the beginning of a paroxysm was obtained. There was the same type of coupling of beats and the complexes during the regular tachycardia were identical in form with the second complex of the couples. Furthermore, the ventricular cycles were approximately equal to the time intervals between the first and second beats of the isolated couples. In Case 4 there was similar coupling and the beats initiating the paroxysm were identical in their relations with those of the isolated couple seen in the same tracing (Fig. 9). Moreover, there are found complexes of supraventricular type more premature than the ventricular complexes, a fact that cannot be explained on the assumption that the abnormal complexes represent merely aberrant beats due to intraventricular conduction changes.

*The Auricular Mechanism During Paroxysms in Cases 2, 3 and 4*—Although no evidence of auricular activity could be discovered in tracings of paroxysms in Cases 2, 3 and 4, there is no reason to doubt that fibrillation continued. Fibrillation was undisturbed by coupled beats in all three cases and by short paroxysms in Cases 2 and 4. In relation to longer paroxysms in Case 2, the auricles were demonstrated to be fibrillating up to the onset of the ventricular tachycardia and immediately after the offset. Fibrillation was also present immediately after the offset in Case 3. Moreover, in Cases 2 and 3, no other auricular mechanism was discovered. A similarly close relationship of fibrillation to paroxysmal tachycardia was also observed in Gallavardin's case.

*The Rhythm of Ventricular Paroxysms*—The fact that slight but definite ventricular irregularity was present throughout the paroxysm in Case 4 does not constitute a valid objection to the interpretation of its ventricular origin. As stated above, a similar irregularity was noted in the short paroxysms in Case 2 and also during the first few beats of the longer paroxysms. The brief paroxysms in Hart's and Cohn's cases also show ventricular irregularity as do the first few beats of a paroxysm recorded by Marvin and White. Thus a high percentage of the cases in which onsets of paroxysms have been recorded, show some ventricular irregularity.



*The Length of Paroxysms*—The length of paroxysms of ventricular tachycardia appears to vary as wide'y as in the supraventricular types. A succession of two ventricular extrasystoles is often found and three occur occasionally. It has not been customary however, to regard less than six successive beats as a paroxysm and these are rare. In about half the cases thus far reported, none of the paroxysms observed exceeded five minutes in duration. Some cases had both short and long paroxysms, and occasionally the tachycardia has lasted for days. The longest case on record is the one reported by Robinson and Herrmann in which an attack lasted presumably for eleven days.

*Association with Myocardial Disease*—It is evident from a study of the cases that paroxysmal ventricular tachycardia is usually associated with grave cardiac disease. Of twenty-two undoubted cases, eleven patients are known to have died within a short time after the ventricular tachycardia was recognized. There is abundant experimental evidence that the condition may be produced by coronary occlusion and Robinson and Herrmann have presented clinical evidence to that effect. Cardiac syphilis has been found in some cases. Occasionally, however, the condition has occurred in patients with a fair degree of cardiac function and without clinical evidences of profound myocardial disease. Most of such cases have been among those with short paroxysms.

*Other Abnormalities of Cardiac Function*—The frequent occurrence of other disturbances of the cardiac mechanism has been a remarkable feature of the cases. Between paroxysms, extrasystoles are usually numerous. Most often these are ventricular in type and have electrocardiographic complexes similar in shape to those of the paroxysms. However all types of extrasystoles may be found. Various grades of *A-V* block up to complete block have been observed and also disturbances in bundle branch conduction. Three of the cases also had paroxysms of supraventricular types of tachycardia, four had auricular fibrillation (including the three of this report) and one, auricular flutter.

*Clinical Manifestations*—Occasionally during brief paroxysms, as in our Case 4, the patient is unaware of anything unusual occurring, but in the majority of cases there are obstrusive symptoms. Palpitation, particularly a consciousness that the heart is beating very rapidly, is most common. In the longer paroxysms, the symptoms of cardiac failure become prominent features. The studies of Barcroft, Bock and Roughton on blood flow and respiration were made in a patient in whom, whatever the origin of the tachycardia, the excitation wave was spreading in an abnormal manner similar to that observed in ventricular paroxysms. These studies show what an extraordinary diminu-

tion of circulatory efficiency may occur during such a paroxysm. It is easy therefore, to understand the seriousness of a long paroxysm of ventricular tachycardia in a patient already the victim of myocardial disease.

As indicated previously, there is no way at present of distinguishing ventricular paroxysms from those of supraventricular type, except by electrocardiograms. From the history and the examination of the heart during a period of rapid rhythm, it should be possible in practically all cases to recognize the presence of some form of paroxysmal tachycardia. One can however scarcely eliminate the possibility (remote as it may be) of paroxysmal auricular flutter. When the paroxysms occur in association with auricular fibrillation, the ventricular action may closely simulate that of an ordinary form of auricular flutter, the paroxysms being mistaken for two to one rhythm and the slower irregular action for the inconstant block that so often occurs in flutter. This happened in our Case 3 and the clinical diagnosis of flutter appeared to be further confirmed by having the patient sit erect, which sometimes brought on the periods of rapid regular ventricular action thought to be two to one flutter, but was in reality paroxysms of ventricular tachycardia. Although the diagnosis of auricular flutter was also made in Case 2, it is apparent, on reflection, that the occurrence of paroxysmal tachycardia originating below the auricles, should have been suspected. The marked discrepancy in rate between the periods of rapid regular rhythm and the slow irregular action were greater than are to be expected to occur spontaneously as a result of change of *A-V* conduction in auricular flutter. Moreover, the conspicuous coupling of beats during the periods of slow action should have directed attention to the possibility of the rapid rhythm being of the nature of paroxysmal tachycardia.

*The Influence of Drugs*—Recently, several papers have appeared suggesting that drugs such as quinidin and digitalis may be responsible, in certain cases, for ventricular tachycardia. Oppenheimer and Mann<sup>17</sup> state that a patient under their observation twice developed ventricular tachycardia during the administration of quinidin. Lewis, Drury, Wedd and Iliescu<sup>18</sup> report that abnormal ventricular complexes are frequent in electrocardiograms during quinidin treatment and that, in occasional cases, they become very numerous and are then associated with long or short periods of ventricular tachycardia. These authors have published a tracing in which a period of tachycardia was recorded

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<sup>17</sup> Oppenheimer, B. S., and Mann, H. Results with Quinidin in Heart Disease, abstr., J. A. M. A. **78** 1758 (June 3) 1922.

<sup>18</sup> Lewis, T., Drury, A. N., Wedd, A. M., and Iliescu, C. C. Observations upon the Actions of Certain Drugs upon Fibrillation of the Auricles, Heart **9** 207 (April 30) 1922.

and they have stated that they were inclined to view the abnormal complexes not as aberrant forms but more comparable to the abnormal beats which help to constitute digitalis coupling. Levy<sup>19</sup> reports that he has recorded ventricular tachycardia in five out of twenty-five cases of auricular fibrillation treated with quinidin.

Schwensen<sup>20</sup> recently reported two cases that he believed to show ventricular tachycardia as a result of the administration of digitalis. Unfortunately, in one of his cases, no tracing was obtained during the period of tachycardia. In the other case, auricular fibrillation was interrupted by a regular tachycardia, the tracing of which showed a remarkable alternation of complexes. The author's assumption of their ventricular origin cannot, however, be accepted as established.

Of the four cases we report, tachycardia due to digitalis or quinidin can be ruled out in Cases 1, 2 and 4, since neither of these drugs had been taken when the tachycardia developed. This is noteworthy particularly in Cases 2 and 4 in both of which accurate coupling of beats occurred. It should, however, be emphasized that this is not necessarily a digitalis effect. We have observed it also in other cases not under the influence of the drug. In Case 3, the possibility that digitalis caused the tachycardia could not be excluded, since treatment has been received before admission to the hospital. This, however, seemed unlikely, as large doses of the drug were administered in the hospital, in spite of which no paroxysms were observed after the second day.

In view of the observations of Oppenheimer and Mann, Lewis, and Levy on the ability of quinidin to evoke ventricular tachycardia, it is of interest to note that quinidin and quinin have been found of value in suppressing the condition. Boden and Neukirch<sup>21</sup> state that they were successful in terminating paroxysms by the intravenous injection of quinidin, while Singer and Winterberg<sup>11</sup> obtained good results in their cases with quinin. In our Case 4, both the auricular fibrillation and ventricular tachycardia were abolished by quinidin. These results would appear to indicate that further observations of the effects of the cinchona alkaloids in this condition are desirable.

#### SUMMARY

1 Four cases of paroxysmal ventricular tachycardia are reported, one with auricular mechanism of normal type and three with auricular fibrillation.

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19 Levy, R. L. The Clinical Toxicology of Quinidin, abstr, J A M A 78 1919 (June 17) 1922

20 Schwensen, C. Ventricular Tachycardia as the Result of the Administration of Digitalis, Heart 9 199 (April 30) 1922

21 Boden, E., and Neukirch, P. Klinische und experimentelle Beobachtungen über die Herzwirkung des Chinidins, Deutsch Arch f klir Med 136 181 (June) 1921

2 The electrocardiographic findings through which the diagnosis was arrived at in these cases are discussed. Emphasis is placed on the value for diagnosis, when the auricles are fibrillating, of comparing the relations of coupled beats to the onsets of paroxysms.

3 The literature is reviewed and from the study of the cases previously reported together with those here presented, the following data have been assembled. (a) Twenty-two cases have thus far been reported in which electrocardiograms justify the diagnosis of paroxysmal ventricular tachycardia. (b) During paroxysms, the following types of auricular action have been recognized: (1) normal mechanism, (2) retrograde auricular beats, (3) auricular flutter, and (4) auricular fibrillation. (c) Slight irregularity of rhythm just after the onset of paroxysms is not unusual. It may also occur just before the offset. (d) In about half the cases reported, none of the paroxysms observed exceeded five minutes in length. The longest paroxysm reported apparently lasted for eleven days. In long paroxysms, severe cardiac failure usually occurs. (e) Profound myocardial disease is usually associated. Other disturbances of the cardiac mechanism are remarkably frequent. Eleven of the twenty-two patients are known to have died shortly after coming under observation. (f) Short paroxysms occurring during auricular fibrillation may cause the ventricles to behave in a manner simulating auricular flutter and lead to a mistaken diagnosis of flutter. (g) The results of quinin and quinidin in treatment have been promising, but further observations are necessary in order to determine whether or not these drugs are of real value in this condition.

NOTE.—Since this paper has gone to press, another case has been reported by Gallavardin (*Extra-systolic ventriculaire a paroxysmes tachycardiques prolonges*, *Arch d mal du cœur* **15** 298 [May] 1922), in which were recorded brief successions of extrasystoles and long attacks of tachycardia, both apparently arising from the same focus. During the long paroxysms, the auricular action was sometimes independent, and at other times controlled by retrograde conduction from the ventricles.

# THE SURGICAL TREATMENT OF ANGINA PECTORIS

WALTER B. COFFEY, M.D., AND PHILIP KING BROWN, M.D.

SAN FRANCISCO

In 1920 Jonnesco<sup>1</sup> reported the cure of a case of angina pectoris by resection of the left cervical sympathetic system under local anesthesia

The patient was a male, aged 38, who gave a history of syphilis, abuse of alcohol and tobacco. He was seen March 19, 1916. First attack, Dec 19, 1915. Violent palpitation, acute pain in precordial region, radiating to left arm, tightness of chest, fear of death. Duration one hour. January, 1916, he had a second attack. After this mercury treatment had no effect. March 14 and 18, third and fourth attacks. Examination showed no tabic or pre-tabic symptoms. Wassermann positive. Heart and aorta enlarged. Pulse, from 42 to 52, an arrhythmia every ten or fifteen beats not recorded on electrocardiogram. Lungs, temperature, abdomen, urine normal. Patient feels well in intervals of attacks. Fifth attack while in hospital. Heart beat rapidly and violently. Face pale, after a few minutes pallor gives way to cold sweat.

Operation April 2, 1916, under local anesthesia. This he accomplished by an injection between the first and second dorsal vertebrae of a solution of 0.02 gm. stovain and 1 mg. strychnin. Resection of the left great sympathetic from base of neck into thorax including two last cervical ganglia and first thoracic ganglion. It is not made clear whether the cardiac branch from the superior cervical ganglion was severed or not. Traction on and avulsion of the first thoracic ganglion caused intense pain in the left arm "like electric shock running into fingers." Following operation there was diminution of the left palpebral fissure, extreme diminution and fixity of the left pupil, retrocession of the left eye into the orbit, although the superior cervical ganglion was not touched. Pulse went from 44 to 52 before operation to 56, and on the third day it was 68 where it remained as long as he was in the hospital (two months).

No further attacks. Refused extirpation of right sympathetic because he felt well without it.

Patient returned April 3, 1920, four years later. No further attacks. Had no antisiphilitic treatment. Pulse regular, from 72 to 74. "Radioscopic examination shows slight dilatation of aorta, with the wall thickened and irregular, with atheromatous spots, and with thick and visible deposits, more marked toward the beginning of the ascending portion. Diameter of heart enlarged 2 or 3 cm. Left palpebral fissure diminished, pupil contracted, eyeball sunken, facial asymmetry. Asymmetry looks at first glance like atrophy, but is not."

F. Franck<sup>2</sup> established relations between irritation of cardio-aortic plexus and the more or less distant manifestations reproducing symptoms seen in angina pectoris. He suggested resection of the cervical thoracic sympathetic for the relief of angina but did not do the operation.

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1 Jonnesco. Bull. de l'Acad. de med., Par 84 93 (Oct.) 1920, also Presse med. 29 193, 1921.

2 Franck. Bull. de l'Acad. de med., May 30, 1899.

Jonnesco regards angina as a manifestation of irritation of the cardio-aortic plexus, in fact, a neuralgia of the same. Gilbert, Gairner and Vaquez approve this theory. Jonnesco's argument is: A more or less marked chronic aortitis is always present in angina. The aortitis irritates the nervous filaments of the plexus. Franck has shown the predominant rôle of sensory fibers ascending from the cardio-aortic plexus, passing to the cervicothoracic sympathetic and reaching the medullary and brain centers by three routes: (1) The paravertebral chain, (2) vertebral nerve, (3) communicating dorsal branches of first thoracic ganglion. There are, therefore, in the cervicothoracic sympathetic centrifugal and centripetal nerves which transmit to the centers impressions arising in the thoracic and even in the abdominal viscera. This explains how irritation of the cardio-aortic plexus causes reflex circulatory, sensory and motor troubles.

To stop these troubles one must interrupt connection between aorta and nervous centers reacting to the irritation mentioned. It would be ideal to cut only centripetal nerves leading sensation from cardio-aortic plexus to brain and medullary centers. This being impossible one must resect the whole strands and ganglia which surround both centripetal and centrifugal fibers. Simple section is insufficient, one must resect. The whole mass of the two lower cervical ganglia and the first thoracic must be taken. Resection of the upper cervical ganglion is not necessary. If the reflexes from the cardio-aortic plexus are suppressed, their consequences, which constitute the alarming and grave symptoms of angina, will be stopped. The sudden death from angina seems to be due to spasm of the arteries of the medulla. The origin of this spasm lies in the aortic irritation.

Vasoconstrictor action of the cervical sympathetic on the bulbar vessels by way of the vertebral nerve is well known. This action is suppressed by the section of the vertebral nerve which takes place when the cervical thoracic ganglion is resected.

Unilateral resection (left) was sufficient in this case. Angina neuralgia is limited to the left side of the thorax and to the left arm. Judging from the brilliant result in this case, Jonnesco is inclined to think that unilateral resection might be sufficient. However, the operation being simple and innocent, it seems preferable to him in future to practice bilateral resection even though unilateral resection should show itself sufficient.<sup>3</sup>

In the medical service of the Southern Pacific Hospital there is a high percentage of cardiovascular cases and angina is an unusually

<sup>3</sup> In April, 1922, Jonnesco published an article on the operative technique of resection of the cervical sympathetic with twelve plates illustrating the incision, the instruments necessary for doing the operation and the appearance of the part after dissection (*Presse méd* 30 353 [April 26] 1922).

common symptom As the hospital is operated to keep the employees in fit condition and to minimize the loss from overturn, many patients come to the hospital even from a distance for a survey of their physical condition because of symptoms which are in any way unusual They are sent in also by their superior officers for symptoms suggesting the likelihood of sudden impairment of their usefulness When Jonnesco's article appeared there were a number of mild angina cases in the wards, and several patients had had severe attacks After consultation with the senior surgeon it was determined to select a case with a long history of attacks, and try the operation under general anesthesia, beginning with the severing of the main trunk of the left sympathetic, and cutting the vertebral connections of the superior cardiac branch from the superior ganglion

As the operation is based upon a theory in support of which experiment on animals is of no value, both because we cannot reproduce the disease in animals and because the nerve supply to the heart is quite different from that in man, it goes without saying that the operation was undertaken only after mature deliberation and frequent consultation It so happened that the most aggravating case (Case 1 in our series) had been observed for a year or more by Dr Herbert C Moffitt, during which time the patient got slowly worse, inasmuch as the attacks became more frequent and more severe It was with great relief that, after a consideration of the operation in which the patient laid the facts before Dr Moffitt, he heartily concurred in this trial

In view of the extreme uncertainty about the sympathetic cardiac connections in man, and with full recognition of the fact that we were proceeding on a theory, after numerous dissections by one of our interns, Dr Unsinger, under the supervision of both of us, we determined to do the first operation in two steps and to do it under general anesthesia The patient was having from six to ten attacks a day under the slightest provocation so that we were unwilling to try the local anesthetic method

The statement usually accepted among physiologists is that the sensory fibers for the heart run through the upper thoracic nerves to the stellate ganglion These fibers have their source of origin in the spinal ganglia and according to Edgeworth<sup>4</sup> and Ranson and Billingsley they pass without interruption through the sympathetic ganglia to end in the heart and main blood vessels Whether any fibers run as high as the superior ganglion is uncertain Believing that there was ground for attributing the attacks in Case 1 largely to stimuli from the brain, although they occurred also after eating, we determined to

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4 Edgeworth J Physiol **13** 261, 1892, J Comp Neurol **29** 405, 1918

sever the upper end of the sympathetic trunk in the first operation, cutting the superior cardiac nerve, and the main trunk of the sympathetic below the superior cervical ganglion. In spite of the fact that many physiologists agree that the cervical sympathetic ganglia have no connection with the brain and spinal cord, except through the sympathetic trunk and the white rami of the thoracic nerves which connect with the cervical sympathetic through the lower cervical and first thoracic ganglia and thoracic cord, the attacks in this patient ceased immediately after cutting the connections above this point, and none

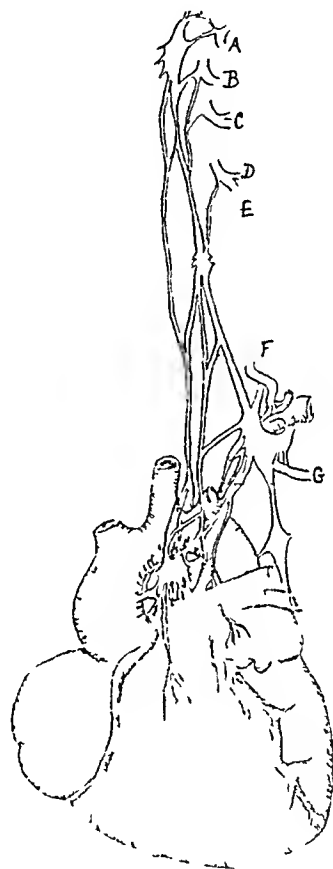


Fig 1—The cervicothoracic sympathetic nerve supply to the heart in man (after Francois Franck) *A*, second pair of cervical nerves, *B*, third pair of cervical nerves, *C*, fourth pair of cervical nerves, *D*, fifth pair of cervical nerves, *E*, superior cardiac nerves, *F*, middle cardiac nerves, *G*, inferior cardiac nerves

have occurred in the eight months since the operation. What is generally accepted as the main connection from the heart to the brain remained intact.

In a personal communication through Dr Herbert M Evans, Dr S W Ranson, professor of physiology, Northwestern University Medical School, states "The removal of the inferior cervical and first thoracic ganglia should be the most effective procedure in the elimination of cardiac pain." It was therefore proposed by one of us (W B C)



to make this the next procedure, provided the severing of the upper connections did not suffice. Although Ranson believes that the cervical sympathetic ganglia have no connection with the brain and spinal cord except through the sympathetic trunk and white ramus of the thoracic nerves<sup>5</sup> the fact remains that in all of our five cases the sole procedure has been the cutting of the direct connections between the heart and the superior cervical ganglion. We believe that by this severing sufficient change takes place in both heart and brain to prevent attacks in cases in which the symptoms are left sided.

Attacks of pain confined to the right side are described by many writers but are certainly very rare. Allbutt<sup>6</sup> reports only one case in which the pain was limited to the right side. No necropsy was obtained in that case.

Morrison<sup>7</sup> reports a case of dextral radiation in which the post-mortem showed gross lesions of the pulmonary valve and the base of the pulmonary artery, the aortic side fairly free from disease. Drummond<sup>8</sup> argues for left sided pain when the aneurysmal sac springs from the anterior aspect of the arch, whereas the nearer the sac approaches the upper and posterior aspect of the inside of the transverse portion of the arch, the greater the tendency to pain in right shoulder and right arm. "One of the most interesting and constant observations was the connection between the root of the innominate artery and pain at the back of the neck and occiput."

It would be interesting to try the operation in a case of dextral radiations, first doing the severing on the right side to see if that would relieve the symptoms. It would be a further contribution to the understanding of the physiology of the sympathetic system if we were able to operate on the inferior cervical and first thoracic ganglia in Case 4 to see if the remaining pain attacks in the left forearm were relieved.

**CASE 1—History**—H B, aged 51, American born, locomotive engineer for the Southern Pacific Railroad Company for twenty-seven years, entered the hospital, Sept 10, 1920 complaining of shortness of breath for three years, more marked for the last six months. Associated with it there had occurred slight precordial pain. He is a very nervous man suffering with headaches which developed after he stopped drinking coffee. His only other subjective symptom was nycturia also of recent date, and an attack of Bell's palsy from which he had not quite recovered, the right lid drooping slightly and the mouth opening better on the left side. He had been well otherwise all his life save for a neisserian infection thirty years ago.

**Physical Examination—First Admission** Slight right scoliosis in thoracic region. Rate and rhythm of the heart normal, second aortic sound markedly accented. Heart slightly increased in size. Blood pressure, 174/85. Wasser-

5 Ranson and Billingsley. *J Comp Neurol* **29** 367, 1918.

6 Allbutt. *Diseases of Arteries Including Angina Pectoris* **2** 301.

7 Morrison, A. *Tr Path Soc Lond*, 1872, *Lancet* **1** 51 (Jan 8) 1910.

8 Drummond, D. *Brit M J* **1** 580 (June 13) 1908.

mann negative. Urine tests showed a phthalein output of 55 per cent. In the test specimen were found a few hyaline casts of varying diameter. There was a lowered ability to concentrate.

He had been told by a heart specialist that he had an enlarged heart. The doctor put him to bed and discharged him three weeks later with a normal blood pressure and the statement that roentgen ray and physical findings showed no arteriosclerosis. But with the return to normal blood pressure his dyspnea had increased. We noted that as his pressure fell again under diet and rest, his nycturia was constant, his dyspnea worse and on any exertion he complained of a "pressure weight sensation" just above the left breast. He felt perfectly well at all other times.

His pulse was never above 78, and after six days of rest his blood pressure reached 147/82. His stomach was larger than normal and he had more gas than usual while at rest. A diagnosis of moderate interstitial nephritis with anginoid symptoms was made.

He returned for three days on March 21, at which time his phthalein output was 70 per cent, pulse from 70 to 76. His nycturia was unchanged and the urine under concentration test was again regarded as abnormal. The blood pressure dropped from 160/80 to 130/70 the third day of rest.

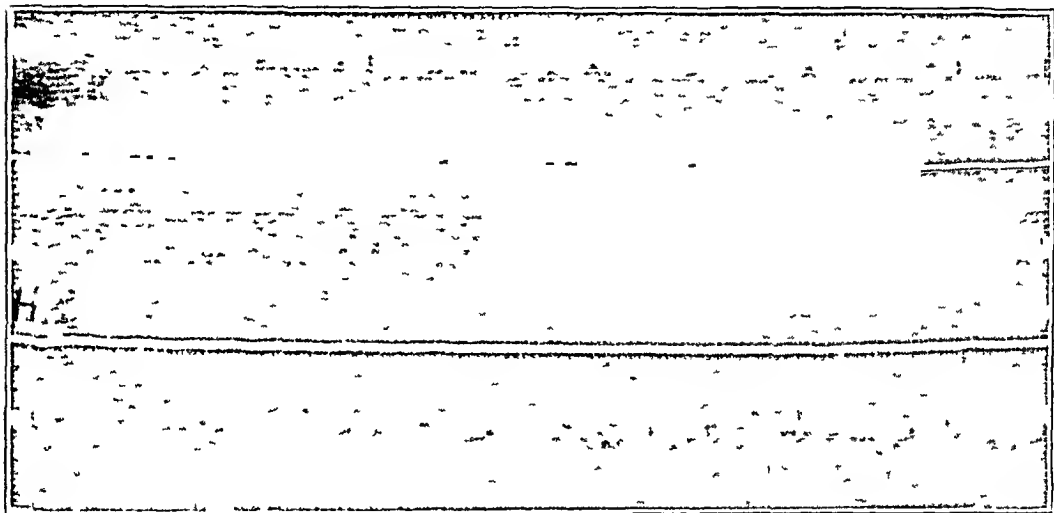


Fig 2—Electrocardiogram of Case 1

*Second Admission*—Oct 15, 1921, the patient was again admitted complaining that for three months he had grown rapidly worse and that he had been under another physician's care since May. A trip to Honolulu, prescribed for rest had made him worse and he now suffered from six to nine attacks of substernal pain a day which were relieved in about five minutes by  $\frac{1}{100}$  grain nitroglycerin. Attacks are precipitated by exertion, excitement and always by eating. He had as many as ten a day and rarely less than six. These had continued for at least three months. An attack was precipitated by examination. In it the pulse rose to 128. Blood pressure, 165/128.  $\frac{1}{100}$  grain nitroglycerin relieved him in a few minutes and pulse fell to 92 and was of much better volume. The same thing had happened on being examined the previous night. He had no attack in the interval but had an icebag over his heart part of the time. He had about six attacks during the previous day. Blood pressure immediately after the attack was 155/104, and five minutes later it was 144/104.

*Course*—October 19. No attack for forty-eight hours. No medication.

October 26. Discovered yesterday that by sitting up when an attack threatened, it passed off. He thinks this was confirmed three times in one day, but it proved later to be of minor value.

October 27 Had four attacks during sleep last night and one this morning after breakfast Has been quite free from attacks for some days Was trying the effects of varying diets and yesterday was put on hydrochloric acid and nux vomica In attacks pulse rises from about 80 to 110 Blood pressure at 9 a m, two hours after meal, 144/80

October 28 Is to continue hydrochloric acid and nux vomica, half a dose after meals and strontium bromid, 15 grains, half an hour before breakfast and supper

October 29 Three attacks in the night last night at 8 11 p m, and 5 a m Bowels moving well with cascara and oil

October 30 No attacks

October 31 Two attacks yesterday afternoon and evening, three in the night and two before 9 o'clock this morning Discontinued hydrochloric acid and nux vomica and gave  $\frac{1}{2}$  grain sodium nitrite and 15 drops tincture digitalis, three times a day, with an order that the patient should not know the nature of the medication

November 2 No attacks yesterday but three in the night last night

During the month of November and up to the time of operation, November 30, the patient continued on small doses of digitalis and sodium nitrite for two weeks He then was without anything for two weeks The attacks average two or three a day Some days there were none and there seemed no difference between the periods of medication and being without it

After we had made numerous dissections on cadavers, we concluded, from the lack of intimate knowledge of the physiology of the sympathetic system in the human being, that we could contribute more to the scientific understanding of both function and results if we did the operation in steps

We, therefore, agreed in spite of the experiments on animals to the contrary, that if the cervical sympathetic excited or controlled the phenomena producing angina, instead of a wholesale dissection, which in no way proved the case, we would first sever the important cardiac connections, beginning at the more accessible end

In doing this, we recognized fully that physiologists claim that the sensory fibers for the heart have their origin in the spinal ganglia and run through the upper thoracic branches to the stellate ganglia There is no proof that any branches reach as high as the superior cervical ganglia The operation we performed, however, demonstrated that the theory is not correct

Our first effort in this work was to do as little as was consistent with the possibilities of relief, not going as far as Jonnesco, and then await results

The report by one of us (P K B) we believe, justifies the theory that the procedure of cervical sympathectomy should only be followed when there has not been a complete or satisfactory relief of the symptoms from medical treatment We (W B C) would not hesitate, with our present knowledge of the operation, to do it under a local anesthetic, when the patient has but mild attacks, precipitated by nervous conditions or disturbances of digestion, or in those cases which occur without known cause, or when the patient has been given the proper medical

attention and rest previous to surgical procedure, but without any relief. No surgeon should undertake this operation without his patient first being in the hands of a careful internist, who watches every detail of the case previous to and following the operation.

#### DESCRIPTION OF OPERATION

An incision is made on the left side, at the posterior border of the sternocleidomastoid muscle, extending from the mastoid prominence along its border to where the external jugular vein crosses this muscle. If it is necessary to go further, the external jugular can be ligated, and the branches of the superficial cervical plexus severed. Then the incision passes through the posterior border of the sternocleidomastoid muscle.

In order to avoid the branches of the auricular and occipital nerves the fibers are separated a short distance from the posterior edge. Dissection in the upper end of the posterior triangle, at the margin, is often difficult. It is easier to separate the fibers, avoiding the nerve, and, in most cases the external jugular. After separating the fibers, the posterior sheath is opened, which is likewise severed (similar to the line of the separation of the fibers). Just below the fascia is a fatty areolar tissue. At the lower angle of the incision, there is a clear space in which blunt scissors are placed, and this area of fatty tissue is widened with the fingers. There is encountered the neurovascular bundle, that is, the deep jugular vein, carotid artery, pneumogastric and phrenic nerves and a branch of the hypoglossal nerve. With a retractor, pulling the muscle and the neurovascular bundle toward the center of the body, the vertebral plane is exposed. Then the field of operation is enlarged and a good view obtained.

In order to facilitate matters, a retractor is placed in the upper angle so as to raise forcibly the muscle and the neurovascular bundle. In this way, the culdesac is easily cleared. (Use of an electric light will give a better view.) Then begins the search for the sympathetic trunk, which rests on the vertebral plane, hidden in its own sheath—thin, transparent and attached to the aponeurosis of the neck. The superior cervical ganglion is a swelling of the trunk, usually spindle shaped. It lies in front of the transverse processes of the second to the fourth cervical vertebrae on the prevertebral fascia and the longus capitis muscle, adjoining the internal carotid and laterally the vagus nerve.

At this point of the operation Jonnesco calls attention to the fact that frequently the sympathetic trunk may rest on or become attached to the neurovascular bundle. One might easily pull it aside with the retractor so it is necessary to proceed with much attention to the search for the sympathetic trunk and not be confused by the phrenic nerve,

which is often very near the sympathetic nerve, or a branch of the hypoglossal nerve accompanying the internal jugular, or still more extraordinarily by the pneumogastric nerve

The confusion that one is apt to find oneself in, especially if retraction is made too soon, or any slight hemorrhage occurs, may make the first efforts in finding the sympathetic very trying. It is necessary always to have some point of reference to orientate oneself and find more easily the sympathetic cord, of which the superior cervical ganglion is the unit and should serve as a guide in finding the main trunk.

When in doubt, the ganglion should be sought on the vertebral plane, at the upper extremity of the field of operation. It is fusiform in shape, and when outlined is very striking. The balance of the work is made easier, if the ganglion is found at once. At the lower extremity of the field the cord therefrom is isolated and seized with a forceps and severed, likewise, the cardiac branches.

In the removal of the ganglion, with the disengagement of the trunk, the ganglion is elevated and can readily be dissected. With a tractor, the ganglion is separated from the neurovascular bundle and freed from the vertebral fascia. The branches, which are attached to the two borders, are cut with a blunt pair of scissors in a manner so that the ganglion is now held by both ends of the cardiac trunk below and the cranial branches above. To remove it in its entirety, it is secured with a hemostat after separating the trunk and cardiac branches. With traction, it can be pulled from its cranial attachment.

This complete removal was done in one instance, and in the other cases, merely the main trunk below the ganglion and cardiac branches were severed.

The wound is closed in the usual way without drainage.

*Postoperative History* (Case 1)—Dec 1, 1921. The patient is doing very well but has elevation of temperature. Heart rate still rapid. Blood pressure 130/80 at 9 30 a. m. Patient states that he has a feeling of impending attack but has had none so far. He complains of pain in the mediastinum unlike that of the attacks. More than likely this pain is due to a gastric condition from the anesthesia.

December 2. Blood pressure 112/70 at 8 30 a. m. Discomfort in precordia and mediastinum has disappeared. Patient is cheerful and is in no way disturbed. Pupils equal and alike on both sides. Temperature 100 F.

December 3. Patient gradually improving. He is rather nervous and has a slight pain in the right axilla (due to ether anesthesia) which he is rather inclined to interpret as still a part of the old condition. Temperature improving. Pulse 104. Blood pressure, 115/69.

December 4. Patient continues to feel better. Pulse gradually coming down—100. Blood pressure 115/70. Feels fine but still seems to pay a great deal of attention to every little thing concerning the left side. Pupils so far have been equal.

December 5 Pulse, 98, blood pressure, 109/68, temperature, normal. Feels fine. Says he feels good enough for a foot race. Has not had an attack of angina so far since the operation. Had a good sleep, slept all night.

December 6 Patient up and about. Feels fine. Pulse, 96, blood pressure, 112/70. Has some gastric distress at times.

December 7 Patient had a slight attack of gastric indigestion which he is inclined to interpret as an anginal attack. However he says there was no pain associated with it. Pulse, 94, blood pressure, 110/68.

December 15 Patient has been up and about for the past ten days. Eats usual diet. Had gas distention of stomach until he began exercise one week ago. Digestion is now all right but he has to take a physic (cascara and hydrocarbon oil) every night. He complains of a slight pain in the left shoulder since the operation. More like a slight lameness. Has had it before operation. It is like a tired feeling from carrying a heavy load. Since the operation, he notices a slight stiffness in the left side of the face beginning at the hair line on a level with the upper ear and extending downward and forward along upper line of hairy part of face to a point almost at left chin, then down neck to middle of sternocleidomastoid muscle and up to lobe of ear. Testing this area with cotton the lobe of the left ear is anesthetic and a small area about one-third the size described by him is subjectively numb. The area extends along the line of the wound but is limited to the anterior part and extends very slightly below the lower limit of the wound and over an area making the segment of the circle 3 cm in radius with the angle of the jaw as center. The upper limit of the wound behind the ear is anesthetic, anterior to it as high as the level of the inner ear. A pin prick in this area feels like a finger. There is diminished sensation to cold over this area and heat is only felt as pressure. The pupils are equal and react normally. No change in color of face. No unilateral phenomena of any sort. Pulse, 96. His phthalein output is 55 per cent. Blood pressure, 165/128. Urine showed the same low specific gravity and inability to concentrate on dry diet.

Jan 4, 1922 Patient returns after two weeks reporting that since he went home he has had no typical attacks but (1) after slight exertion he feels a shortness of breath as if his throat were obstructed but not actually interfering with the breathing. Has it a good deal of the time because every exertion produces it. Once after he had had it for four hours and could not lie down because it got worse, he took  $\frac{1}{100}$  grain nitroglycerin and was relieved in a few minutes. (2) Has lameness of left arm with stiffness in shoulder and pain above the joint when he moves it. No pain when at rest. This is an old trouble but he thinks it came on after the sympathectomy. (3) Pulse about 86. (4) Numbness in left cheek is less extensive. Feels touch on upper half of ear. Anesthetic area the size of a dollar at the angle of the jaw and between that and upper half of surgical incision. (5) Eating has produced none of the symptoms which he used to have, distinct anginoid attacks frequently following meals, but almost always substernal distress and sense of pressure. Nycturia once, which is his rule for past year. Blood pressure, 132/80. Was 110 when he left here and prior to operation had reached 184 and averaged above 160. Rhythm of pulse not normal.

CASE 2—History—P. R., aged 62 driver of electric truck, was admitted to the Southern Pacific Hospital Nov 10 1921, for an acute attack of pain in the left chest one week previously. The pain was described as a viselike grip beginning under the sternum and radiating somewhat to the left side. According to his wife's account he fainted and was unconscious for several minutes. There was decided dyspnea and cyanosis during the attack and both dyspnea and orthopnea on exertion after it. In the following week there were eight attacks, the last three being more severe than the others. For the past few days air hunger has been increasing.

*Physical Examination*—Patient presented marked cyanosis, especially of the ears cheeks and lips, irregular pulse, 42 pulse deficit, countable beats at wrist numbering 88, poor quality to heart sounds, which were described as distant. Heart markedly enlarged in both directions, aortic area increased also but no thrill felt. Blood pressure, 240/130. No edema of the extremities. Liver large and tender, but not pulsating. Urine normal, but concentrated. Wassermann negative.

*Course*—He was given digitalis in full doses with sodium nitrite, calomel and salts, Karel diet and absolute rest. During the next five days his blood pressure fell to 200/130 198/128, 145/100 135/90. It then rose to 178/100 and did not fluctuate much from this point until the left cervical sympathetic system was interfered with when it fell to 160/110 and has varied but little since then.

The anginal attacks after entrance occurred on the third night, the eighth night the thirteenth night and the morning of the seventeenth day. The first two began during sleep and were slight. Alkaline salts followed by the belching of gas relieved the second one. The third occurred while he was on his

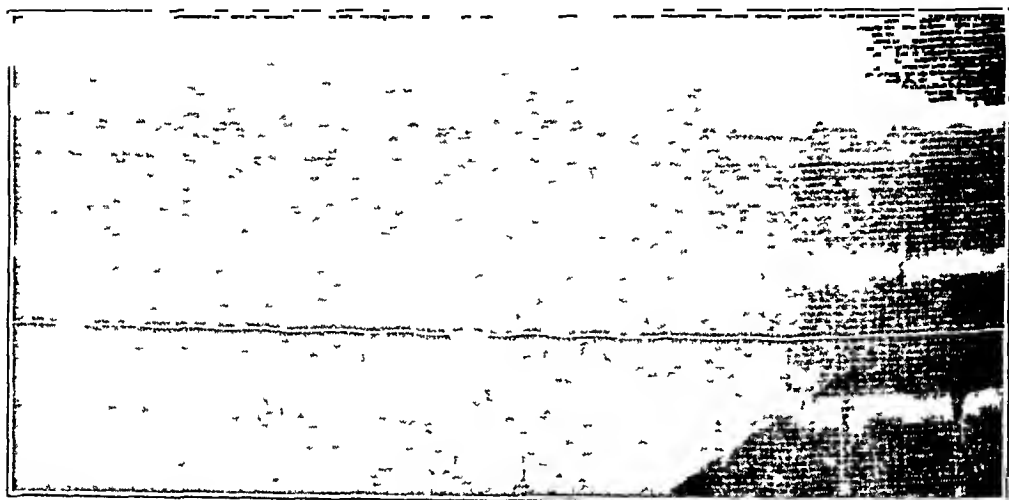


Fig 3—Electrocardiogram of Case 2

feet to urinate and was more severe. Pain began above the heart to the left of the sternum and lasted one-half hour. Sudden nausea ten minutes after pain began was followed by vomiting of bitter clear fluid, with some relief of pain. He stated that some nausea usually accompanied attacks. No dietary error preceded the attack, sleep had been sound and the only unusual event was his getting into the erect position to urinate. The last attack was again slight with distress in the upper epigastrium and no substernal pain. Twelve hours after this he vomited a number of times a bile stained fluid. At this point it was discovered that two years before he had had what was regarded as a "stomach attack." The pain was under the upper sternum and resembled the pain in the present attacks and was probably a true angina.

*Radiologic examination* of the gastro-intestinal tract gave the following information. "The stomach is normal in size, outline and position and contains no filling defects. The duodenal cap is normal. There is a constant spasm of the gallbladder. The barium meal had passed normally in less than six hours. The appendix did not fill. A rounded shadow resembling a thickened gallbladder is seen under the edge of the liver. The heart is enlarged laterally to a marked degree but there is no arteriosclerosis of the aorta."

*Operation*—December 9, under gas oxygen anesthesia, preceded by an injection of  $\frac{1}{6}$  grain morphin and  $\frac{1}{480}$  grain atropin, the left cervical sympathetic system from the superior to the middle ganglion was exposed (W B C) and the main trunk and the superior cardiac branch severed

*Course*—There were no eye symptoms following the operation. The pulse deficit was so irregular that any change in heart action immediately following the operation could not be determined. The rest in bed following the operation improved the heart action and when the patient left the hospital two weeks later he was free from any symptoms save a numbness of the cheek below and in front of the left ear and between the operative wound and the angle of the jaw. He had been taking reasonable exercise for a week and eaten full diet. He spent three hours in saying good bye to old friends who were obliged to remain in the hospital over Christmas and was emotionally and physically much taxed. A slight attack of substernal pain came on just as he was leaving the hospital and lasted fifteen minutes. Patient described it as similar to the preoperative attacks but not as severe as even the mild ones.

An attack of bronchopneumonia confined the patient to bed for some weeks shortly after this, and as his cough was very severe and prostrating, he was

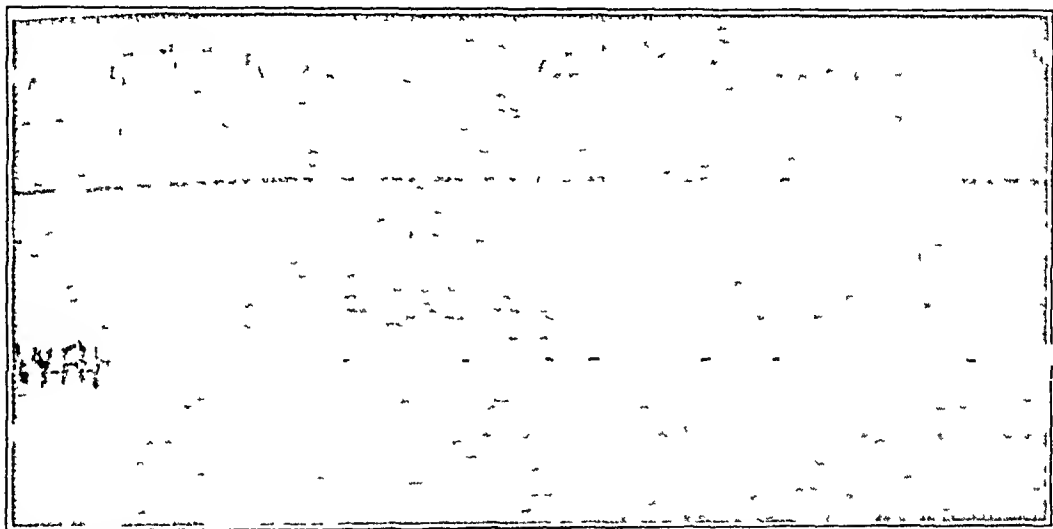


Fig 4—Electrocardiogram of Case 3

brought back to the hospital two months after the operation and five weeks after the bronchitis developed. He was having 2 or 3 degrees of fever every three or four days, great prostration and the right chest was full of râles, especially at the base behind. A roentgenogram showed the remains of a severe capillary bronchitis and congestion at the base of the right lung. The blood pressure was 171/110, marked auricular fibrillation. As digitalis had had but little influence on the fibrillation, quinidin, in  $3\frac{1}{2}$ , 5 and  $7\frac{1}{2}$  grain doses, was tried with no apparent result. Relief of the bronchitis came shortly from iodids and rest.

Patient seen last May 8. He is at work driving an electric baggage truck and doing a full day's work without symptoms of angina or decompensation.

**CASE 3—History**—W R H, aged 54, bridge carpenter, was admitted to the hospital Nov 30, 1921, with a marked decompensation, auricular fibrillation, countable wrist pulse varying from 140 to 160, edema of the lower extremities, to and fro murmur over heart which was enlarged orthopnea. He gave a history of "acute indigestion" eight days before. Had had a cold for three weeks but otherwise was in a fit condition. The attack of "indigestion" was described as a sudden acute pain just below the ensiform cartilage in the



upper epigastrium over an area the size of the open hand. It was dull and boring with acute stabbing intervals, shooting to the left shoulder and down the arm to the elbow, occasionally to the left neck but not to the back. The pain lasted twenty-one hours, and was not accompanied by nausea or vomiting. The pain was exceedingly severe but the patient says he had no "fear of impending death." There was severe dyspnea and evidently some edema of the lungs. The pain was worse when he attempted to lie down, and he could not breathe at all when he tried to lower his head. As he was on a siding with a construction gang no medical aid was available.

There had been no previous attack and his general health had been good since childhood. His teeth were very bad and six months before he had had them all removed. Noticed nothing as a consequence. He had smoked to excess a few years before but not recently at all.

*Examination*—The Wassermann test was negative, urine negative and there was no fever. Blood pressure 106/84 while pulse was above 150, changing to 110/76 when the pulse slowed down to below 100. The irregularity continued during the ten days stay in the hospital.

Patient declined operation which was advised on account of the absence of correctible and possibly etiologic conditions, the severity of the attack and the inability of digitalis to correct the fibrillation.

*Second Admission*—January 17 the patient returned to the hospital with the story that early in the evening of the fifteenth, while sitting up in bed, another attack had come on lasting eight hours, not as severe as the first but followed by the same edema of the lower extremities, rapid heart action and dyspnea. On digitalis and sodium nitrite he improved rapidly, and except for one day of pain in the heart and one day of headache in temples and eyes he had no subjective symptoms. In eight days the pulse was 72, missing one beat in every six to ten, and the blood pressure was 120/80.

*Course*—Drugs were discontinued for five days and then a trial of quinidin was made with no benefit, he was sure it caused dyspnea and severe headache. There were mild anginoid pains for several days a week later.

February 10 he stated he had had pain in the left side of the neck and down the arm, but not severe. His blood pressure, February 15 was 110/70.

*Operation*—On that morning under procain anesthesia the main trunk of the left cervical sympathetic was cut below the superior ganglion. On exposing the left superior cervical ganglion region the ganglion was found to be higher up than usual and although the patient was thin it was difficult to expose its connections, due largely to the absence of anesthesia from procain because of a desire not to interfere in any way with the conductivity and sensitiveness to electrical or mechanical stimulation. Even sponging to clear the field from blood caused the following symptoms: (1) Feeling as if "base of brain" was on fire. Hot burning pain continuous as long as irritation continued. (2) Pain "across the eye" shooting from a point which patient later described as below the mastoid to the eyeball forcing the lid to close (He thinks the upper lid only). (3) Eyeball felt full (Bigger than normal). (4) Some pain along course corresponding to supra orbital nerve and across side of head to a point above the ear. (5) There was no local pain from the sponging or electrical stimulation. The nerves and ganglion were then stimulated with copper wire attached to a dry cell—one pole on a large pad on back of neck. The first application of the galvanism to the largest trunk from the superior cervical ganglion caused sensation in teeth and upper left jaw. There was one occasion when he felt a spasm of the throat could not speak, except in a husky voice, asked for air was nauseated and at the same time felt symptoms in the eye and the base of the brain. This was when the superior ganglion was taken in the teeth of the forceps and pulled on.

At one time he had slight shooting pain in the heart accompanied by contraction of the shoulder muscles without pain.

CLINICAL DATA IN FIVE CASES OF ANGINA PECTORIS

	Age	Sex	Nature of Heart Lesion	Wassermann Reaction	Average Blood Pressure	Complications	Electrocardiograph Report Before Operation	Frequency of Attacks
H B	51	M	Probable myocardial changes in all five cases	Negative	174/85 reaching normal on diet and rest	Probable beginning interstitial nephritis	Numerous ventricular extrasystoles, inverted T in Leads II and III	6-8 a day 1757 hrs 21:40, 11:15
P R	62	M	Auricular fibrillation, hypertrophy and dilatation	Negative	240/130 145/100	Edema of brain on entrance	R is high in I, S is marked in III, auricular fibrillation, left ventricular preponderance	20 attacks, increasing severity and frequency 6:45 hrs, 6:45 hrs
W R H	54	M	Auricular fibrillation	Negative	130/90 110/70	Edema of lungs and extremities from attacks decompensation	Auricular fibrillation	2 attacks without provocation, 1st lasting 21 hrs, 2d lasting 8 hrs
T J	54	M	Syphilitic aortitis with in curysmal dilatation of ascending aorta, mitral and aortic regurgitation	+ to ++ in spite of constant treatment	205/45 190/0 182/32	Syphilis, beginning aneurysm	Inverted T in all 3 leads, serious myocardial disease	Pain every day, attacks every few days 7:15 hrs, 11:15 hrs
T	44	M	Syphilitic aortitis with dilatation of ascending aorta	+++ treatment without effect on attacks	130/60 99/66	Syphilis, beginning aneurysm	Inverted T in Lead III, S marked in Lead III, left ventricular preponderance	10 to 20 a day for 15 weeks, fewer for a year previous

*Course*—After the operation the left pupil was contracted and the conjunctiva reddened

February 23 he complained that during the night before he was awakened twice by burning pain in the "base of the brain" lasting an hour each time. This pain was not as bad as the same pain he experienced at the time of operation. Patient returned to work February 27 to report in one month. The left pupil was still a little smaller than the right. A second trial of quinidin was made after operation but  $22\frac{1}{2}$  grains did not affect the fibrillations. Larger doses were not given because of their previous bad effect.

*CASE 4—History*—T J, conductor, was admitted to hospital, March 7, 1922, for substernal pain following exertion or exposure to excitement or cold.

*Previous History*—Syphilis in 1899. Three plus Wassermann, Nov 14, 1921. Two plus Wassermann, March 1, 1922. Under treatment numerous times for syphilis. Fourteen neo-arsphenamin injections and sixty-six intravenous cyanid of mercury injections. Wassermann never negative.

In 1914 he was told that he had valvular heart disease. Occasionally since then he has had a sharp pain in the heart (thinks it is from gas), but it

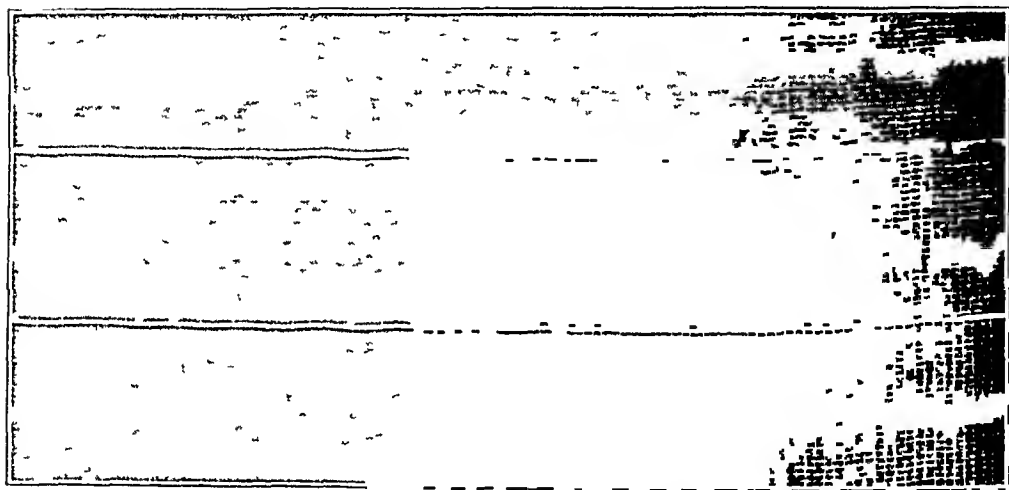


Fig 5—Electrocardiogram of Case 4

radiates to the upper sternal region and down left arm. Feels it especially in left elbow, and flexor surface of left forearm and left hand. The whole arm gets numb. Cannot walk more than five car lengths without pain, especially at night (possibly on account of fatigue). Has taken soda and nitroglycerin with relief he thinks. Since 1915 he has had some pain in region of aorta all the time. A cantharides plaster may relieve this for several days. Has had cough with expectoration since 1915 and always substernal pain with cough. Occasional dizzy attacks, independent of the angina, may come from walking. Has had pain attacks lasting about twenty minutes in left parietal region with the dizziness.

*Physical Examination*—Eyes clear, pupils regular, seem to contract normally. Nose normal. Hearing good in right ear, left slightly defective. Some teeth decayed and need attention. Odor of breath a trifle putrid. Membranes normal. No tonsil enlargement. Tongue clean. Glands not enlarged. Chest Percussion note normal. Expansion fine. No abnormal breath sounds, except occasional catch and click where roentgen ray shows diaphragmatic adhesions at left apex. Heart. Vessels of neck prominent and pulsate. Double murmur heard everywhere. Thrill at apex. Maximum beat fifth interspace outside mammary line. (Both stenosis and insufficiency of mitral valve. Insufficiency of aortic valves.) Rate slightly rapid and rhythm irregular. Substernal dullness

increased and pulsation felt in suprasternal notch No thrill there Genitalia Normal Reflexes Knee jerks not obtained Rhomberg slightly positive Blood Pressure 142/32 Roentgen ray shows diaphragmatic pleurisy and pleuropéricardial adhesions and a shadow thought to be due to a healed lesion at left apex Fluoroscopic examination shows general hypertrophy of heart, aorta thickened, increased in size and marked pulsation which is also expansile in type

*Diagnosis*—Chronic aortitis and a question of beginning aneurysm

*Treatment*—Patient was confined to bed on light diet and antisyphilitic medication March 11, 1922 He frequently awakens in the night with the pain and is conscious, as he was last night, that he had had nightmare Something was chasing him Thinks that walking in the night air or cold air is more apt to precipitate pain Occasional extrasystoles noted

March 13 (Examination by Dr G H Willcutt) "There is quite an amount of purulent material in the lower part of the trachea which is forced upward by expiration and phonation There is a chronic inflammation of the vocal box itself but the cords are not involved Believe the material seen in the trachea is coming from below"

March 16 Walks ten to twenty blocks a day Always has anginoid pain below middle third of sternum and in left neck Worse when he exercises unusually and at night

March 23 Heart rate, 96, rhythm fairly normal Blood pressure 188/32 Had asphenamin at 3 p m yesterday at Municipal Clinic They report his Wassermann as three plus One hour after this injection, he had a moderate attack of angina lasting twenty minutes Pain felt in left side of neck first and then under upper part of sternum and finally in left forearm just below the elbow Hand felt numb No special tingling in fingers as he has sometimes Attack came on as he was returning to hospital The last attack before this was about 7 30 p m on the night of the twentieth as he started back to the hospital This attack lasted one hour, and was quite severe Pain in some places, shortness of breath Felt heart flutter

*Operation*—The operation of left cervical sympathectomy was done (by W B C) under gas and oxygen, March 23 Had an anginal attack lasting twenty minutes just as he reached the operating room Had to stand and lean over to get relief The superior ganglion was unusually high up and when it was pinched with forceps no eye or pupillary reflex was observed in left eye (both pupils were markedly contracted which may have accounted for this) for he was deeply narcotized Pulse rose from 84 to 96 on the operating table but this, too, may have been due to the anesthesia The main trunk of the cervical sympathetic and superior cardiac branch were cut below the ganglion No immediate effect on pulse After the operation, the patient said he could not open his left eye for five or ten minutes Noted slight pain of anginal character under upper sternum for five minutes, coming on shortly after he regained consciousness

*Course*—March 24 No strain now with his cough and no pain with the cough which he frequently had before Pulse, 90 Blood pressure, 196 systolic Left pupil contracted half the size of right Conjunctiva blurred on left side

March 26 Blood pressure, 205/45 Feels fine but twitchingly nervous Coughs less severely, raises easily No pain Gave 5 grains potassium iodid and 15 grains strontium bromid three times daily He thinks now that the pain he had when emerging from the anesthesia was imaginary

March 27 Had a little pain in the flexor side of left forearm last night lasting ten minutes The substernal condition is felt when he takes a deep breath but is wearing off Instead of a lasting burning pain it is now "like a pull on a scar that is no longer sore"

March 29 Yesterday twice and once this morning had a slight pain in left forearm for twenty minutes Cold causes it and he thinks it goes away with warmth

April 6 Yesterday he had neo-arsphenamin, 0.9 gm., and we are giving meicacodal intravenously every day for three doses, then every other day except when he gets neo-arsphenamin. Caught cold yesterday. Has had both substernal pressure and left forearm pain for week past, but only at night when he gets up in the night to urinate. Was on diuretin for one week. Says the bromid sodium mixture makes his head ache and that is to be omitted. The pain in the heart and arm are not as severe by half and last from ten to twenty minutes instead of an hour. Does not have them in the day time.

April 24 Patient has been markedly better since operation. No substernal pain but is sometimes conscious of pressure there. Still has pain in flexor surface of left forearm at times after exertion. Has been emotionally carried away by Revivalist McPherson, who is proving Barnum's dictum, that the public likes to be buncoed. He considers himself cured by her. Has been having daily intravenous injections of mercury at the hospital and arsphenamin at the public clinic once a week, and is still Wassermann positive. Has been up and about for a month and except for slight pain in left forearm, which he feels if cold or tired, he has no subjective symptoms. The cough has practically disappeared.

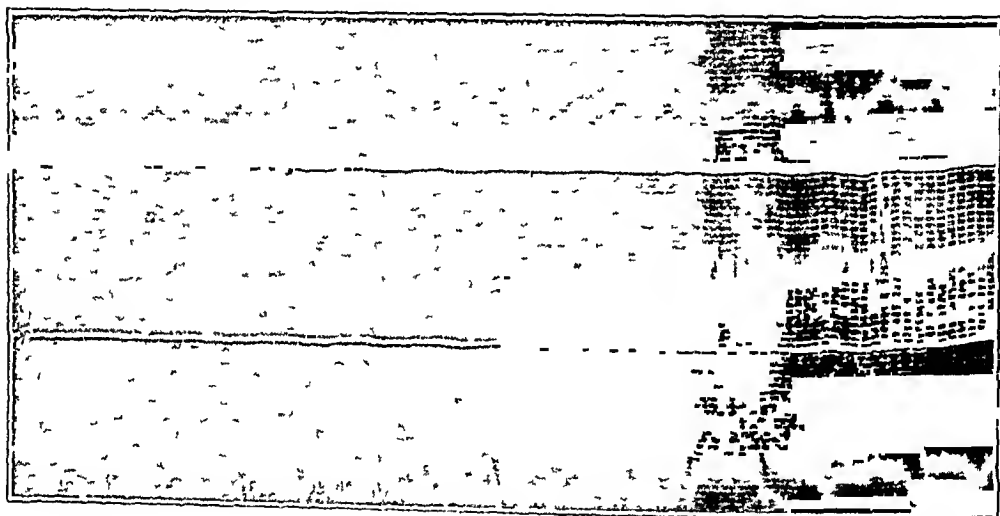


Fig 6—Electrocardiogram of Case 5

CASE 5—*History*—L. J., aged 44, printer, was admitted April 4, 1922, complaining of pain in chest and both forearms beginning about one year ago with intense pain on exertion which left him when he rested a few minutes. Did night work and on the way home the attacks were more likely to come. From the start attacks came about once a day. He began having pain in right forearm very shortly after onset. The substernal pain was not more severe or more frequent and the pain in the right arm was not severe at first. The next development was six months later when the pain came on in the left forearm. It never shot up to the shoulder nor has it been felt in the neck. From the start in the left arm it has been severe everywhere and lasted longer and came more and more often until he consulted Dr. Strietman who put him to bed and gave him iodid and mercury by mouth which later was changed, at Dr. Moffitt's suggestion, to iodid by mouth and mercury rub. Has not done any work for six months. After attacks became severe he went to bed. In spite of one negative Wassermann he was put on mercury rub and given neo-arsphenamin. The rubs were followed by a relief of pain for a day or two. He is not able to distinguish benefit from rest as compared to benefit from medication. For three months was a good deal better. The daily attacks were reduced to two a month, were very severe but were relieved

by nitroglycerin. While on the rubs he was better but stomach was out of order. Neo-arsphenamin upset his stomach more and more, but also relieved pain. Has been without treatment for three or four weeks and attacks are again very severe, about one an hour at night and less often by day. Wife reports that before the attacks began 1 year ago he had a dragging of left toes so that he wore out the toe of his shoe. For three years this had been coming on and getting worse. When tested by Dr. Strietman, during an early examination, an incoordination in left foot was found.

*Past History*—Negative except for soft chancre and Neisserian infections. Inveterate smoker for twenty years. Never had a headache except after alcoholic excesses.

*Examination*—Tongue clean. Teeth sound but tendency of gums to recede. Both tonsils infected, especially the right. Anemic (Pale?) Chest normal in appearance. Lungs O. K. Heart enlarged laterally. Apex in mammary line, fifth interspace, rate and rhythm normal. Double murmur everywhere, presystolic ending in thump, and systolic at apex, but a diastolic is plain to left of sternum in third interspace. A different sort of systolic roughness is noted over aorta. No thrill felt anywhere. Liver not large. No edema. Eye reflexes, normal. Pupils equal and react to light. No numbness in hands or feet but feels a little tingling for two weeks past in fingers and toes, almost constant and aggravated by holding out his hands. No knee jerks. Blood pressure, 130/60.

Röntgen-ray examination of chest (M. P. Burnham). "Six foot plate showed hypertrophy of both right and left hearts, more marked of left with increased density in thoracic aorta as a whole. Arch raised about one inch higher than normal, overlapping lower border of clavicle. Findings typical of aortic valve lesion plus aortitis."

April 5, 1 p. m. Had no attack and no pain from yesterday morning until the doctor came this morning to do spinal puncture. While cleansing the back an anginal attack began with substernal pain, then in both forearms. Never any neck or stomach symptoms. During the night had some sensation of gas in abdomen but had altogether a comfortable night. Had another attack just now when I came into the room. Is fully conscious of the nervous cause of these attacks. After the attack, which lasted ten minutes and was relieved (probably by two doses of nitroglycerin) the blood pressure was 96/66.

*Operation*—April 6. Before operation blood pressure was 122/60. The pulse averaged about 90, it rose to 140 at the beginning of the anesthesia by gas and oxygen and fell to 120 after the operation. The patient struggled so violently that it was necessary to administer ether during most of the operation.

Following the operation he was somewhat cyanotic and his skin was much relaxed. He became conscious very shortly and during the six hours that he lived he had no pain but a distinct vasomotor disturbance, heart acceleration, cyanosis, drenching perspiration with markedly relaxed skin, failing to respond to atropin. He died a cardiac death.

#### SUMMARY

Patients were selected for operation from a large group and only those were operated on whose attacks and pain symptoms were extremely exaggerated, or as in Case 3 the few attacks were of extremely grave character, and the underlying condition not amenable to therapy. The patient in Case 1 had had six months of rest and care with progressive increase of his trouble. The patient in Case 2 had a degree of hypertrophy with probable myocarditis that was

extreme and was very nervous, some of his attacks occurred during sleep. The duration of the attacks in Case 3, twenty-one and eight hours, with more or less constant substernal pain and the fact that there was no dietary error or physical strain preceding the attack, led to the patient's returning to the hospital to ask for the operation. Case 4 was an emotionally unstable person with attacks of seven years duration, and syphilis with a beginning aneurysm of the ascending aorta and advanced valve disease for which there was promise of little or no relief. Case 5 was of the same sort, with the same lesions exactly, except that the attacks were less extensive and of shorter duration. In spite of fifteen weeks rest in bed under able care the patient was having attacks many times a day. The cause of his death six hours after the operation, seemed to be acute vasomotor disturbance with dilatation of his heart. His operation required nearly twice the time the others did on account of the peculiar condition of the superior ganglion which made its recognition difficult. He had lived in a constant state of fear and the shock of the whole procedure was a very serious matter. The operation was hastened because of the expense of hospital care, which the family felt heavily, and in reviewing the facts outlined in the history it is evident that it would have been better to have delayed matters until his nervous system was more stabilized, and antisyphilitic treatment tried further.

The fact that in Case 2 a slight attack occurred a month after the operation requires some interpretation as does the persistence of occasional pain attacks in the left forearm in Case 4. Both these cases offer the interesting possibilities of further relief by the carrying out of the Jonnesco's original plan of the similar operation on the right cervical sympathetic system in our second case, and cutting the connection between the spinal ganglia and the lower left cervical and first thoracic ganglia in the fourth case.

We determined at the outset to do as little as was consistent with the possibilities of relief, and instead of taking out the three cervical and first thoracic ganglia, as proposed by Jonnesco, the operation was limited to the severing of the main trunk below the superior cervical ganglion and the superior cardiac branch. The fact that from two to seven months have elapsed in the four cases in which the operations were successful, with practically entire relief of symptoms, except those enumerated in Cases 2 and 4, justified this conservative course and contributed greatly to the understanding of the problem of angina. That the procedure is possible under local anesthesia puts the operation where it must be considered hereafter in two classes of cases, those in which there are frequent mild attacks precipitated by nervous conditions, digestive disturbances or mild effort, and the class of cases in which there are mild attacks, particularly those which occur without

known cause, and frequently when the patient is at rest. If in these cases proper medical care, including the correction of possible exciting causes, brings no relief, our experience leads us to feel that the operation is a procedure which must be considered.

It is easy to speculate about the actual effect of the operation from the point of view of interference of conduction paths, but it would certainly seem that Allbutt's contention, in so far as it is corroborated by the studies of Vaquez that a spasm of the aorta causes the pain, has considerable proof in these cases. We are unable to follow Allbutt in his view that the vagus inhibition causes the death. The blocking of the coronary system with a thrombus produces an angina in which, of course, there is no spasm and frequently no pain and for which there is no relief. There is proof enough in the voluminous literature that one almost constant accompaniment of death in an attack is the occlusion of the opening of a coronary vessel or the main trunk of a coronary vessel through disease of the aortic walls in the first instance and of the coronary walls in the second. When the pain and spasm are interrupted, the aortitis may not be sufficiently extensive to do any further harm by occluding the coronary vessel. It goes without saying that the blood supply of the heart in cases of extensive coronary disease certainly makes the occlusion from spasm of a diseased aorta all the easier and death more likely. Both Allbutt and Franck contend, however, that death is due to heart inhibition, conducted, according to Allbutt, largely through the vagus, and stimulated by the pain of the aortic spasm. Franck contends that the cervical sympathetic acts as both a constrictor and dilator of the aortic vessels and it has also an action as a cerebral vaso-constrictor. A section of the cervical sympathetic cord increases therefore the flow of blood to the brain. He contends that the cardiac accelerators come from the superior thoracic region very largely, and considers that a total resection of the lower cervical ganglion and first thoracic is necessary in order to control acceleration completely. There is experimental evidence, however, in some minds that severing the cord above the thoracic segments stops acceleration.

Franck contends that the whole sympathetic apparatus, thoracic and cervical, deep and superficial, has a direct sensibility, and transports to the medulla and cervicodorsal cord afferent nerves, coming especially from the aorta. According to Franck's view, it is logical to think that the resection of the sympathetic acts as much in suppressing transmission of abnormal irritation of the cardio-aortic origin toward the brain centers as in suppressing efferent thyroidal, encephalic or cardiac influences. This notion of aortic sensibility transmitted by the thoracocervical sympathetic suggested to Franck the idea of practicing



the resection in angina pectoris. It was seventeen years after this suggestion of Franck's that Jonnesco took it up and did the first operation for the relief of angina.

Concerning the safety of the operation in other than cases of angina, important light may be found in the report by Jonnesco<sup>9</sup> on 159 cases of cervical sympathectomy for the relief of goiter, epilepsy and neuralgia. The operation has been done also for the relief of glaucoma<sup>10</sup>. Of the 159 cases, in 141 three ganglia were removed and in some the first thoracic also and in all but two cases the operation was bilateral. No deaths and no secondary trophic disturbances. Of twenty-five cases of exophthalmic goiter, all the patients made a complete recovery. Of eighty-eight cases of superior sympathectomy, sixty-one patients were cured or improved, twenty-two were unimproved and five were worse. In 117 cases of epilepsy there were twelve definite cures. Of 2 cases of trigeminal neuralgia, one patient was relieved for four years and one for six months.

#### CONCLUSIONS

Sympathectomy was done in five cases of angina pectoris, two of them presumably due to syphilitic aortitis. Death occurred in one case. Marked improvement was noted in the remaining four cases.

In view of the obstinate and painful nature of the symptom angina pectoris, the relief following operation in these cases seems sufficient to warrant further trial of this or similar operative procedures.

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<sup>9</sup> Jonnesco. German Surgical Congress, 1906. Quoted by Binnie.

<sup>10</sup> Binnie. Manual of Operative Surgery, Ed 7, 1916, p 221.

# FATTY DEGENERATION OF THE HEART \*

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The clinical and pathologic diagnosis of "fatty heart" or of the heart the seat of "fatty degeneration" <sup>1</sup> is still too commonly made. A decade ago it was even more frequently diagnosed than it is now. Broadbent <sup>2</sup> described the etiology, symptoms, physical signs, prognosis and treatment of fatty degeneration of the heart. He says, "No form of heart disease is regarded with so much apprehension as fatty degeneration. More than any other, it carries with it the dangers of sudden death and the liability to angina pectoris."

Hirschfelder <sup>3</sup> also described the symptoms and signs of the heart in fatty degeneration. He says, "The most characteristic symptoms associated with the condition are those of general debility and feebleness, more or less languor and somnolence, as a rule, without marked cardio-respiratory symptoms except shortness of breath on exertion. The pulse is usually small, rather collapsing and feeble, the blood pressure is below normal the pulse rate is increased."

We are told that the tone of the cardiac muscle is diminished, that patients with fatty degeneration of the heart are very sensitive to digitalis and are frequently injured by it. Sudden death from overdose of this drug or from acute cardiac overstrain is more common in patients with fatty degeneration of the heart than in almost any other condition, and, finally, that spontaneous rupture of the heart is relatively frequent here.

In summary, however, Hirschfelder, frankly states that none of the symptoms is "either constant or characteristic" and the diagnosis may have to be made by inference only. As Krehl <sup>4</sup> says, there is no clinical sign for the diagnosis of fatty degeneration of the heart.

We believe that the clinical diagnosis of fatty degeneration should be based on etiologic grounds, e. g., in phosphorus poisoning, pernicious anemia, etc. Otherwise, to make this diagnosis during life is very uncertain.

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\* From the Department of Laboratories, Bellevue Hospital, Douglas Symmers, M D, Director.

1 We distinguish here between fatty degeneration of the heart with which this paper deals solely and fatty infiltration in which fat is present beneath the epicardium, or penetrated between muscle bundles even as far as the endocardium.

2 Broadbent, W H. Heart Disease and Aneurysm of Aorta, 1906 p 342.

3 Hirschfelder. Diseases of the Heart and Aorta, 1918, p 312.

4 Krehl, L. Ueber fettige Degeneration des Herzens, Deutsch Arch f klin Med **1** 416, 1893.

It is trite to state that necropsy findings must be, in great part, the criteria on which diagnoses rest. Undoubtedly, then, the frequency of the clinical diagnosis of "fatty heart" is based on the same frequency with which this type of heart is found, postmortem. We are told by the highest authorities that fatty degeneration of the heart is a common pathologic condition.

The etiology<sup>5</sup> is given as alcoholism, primary and secondary anemia, after hemorrhages, associated with myocarditis, valvular and other cardiac lesions, in most infectious diseases, in miners, smelters and many metal workers, etc.

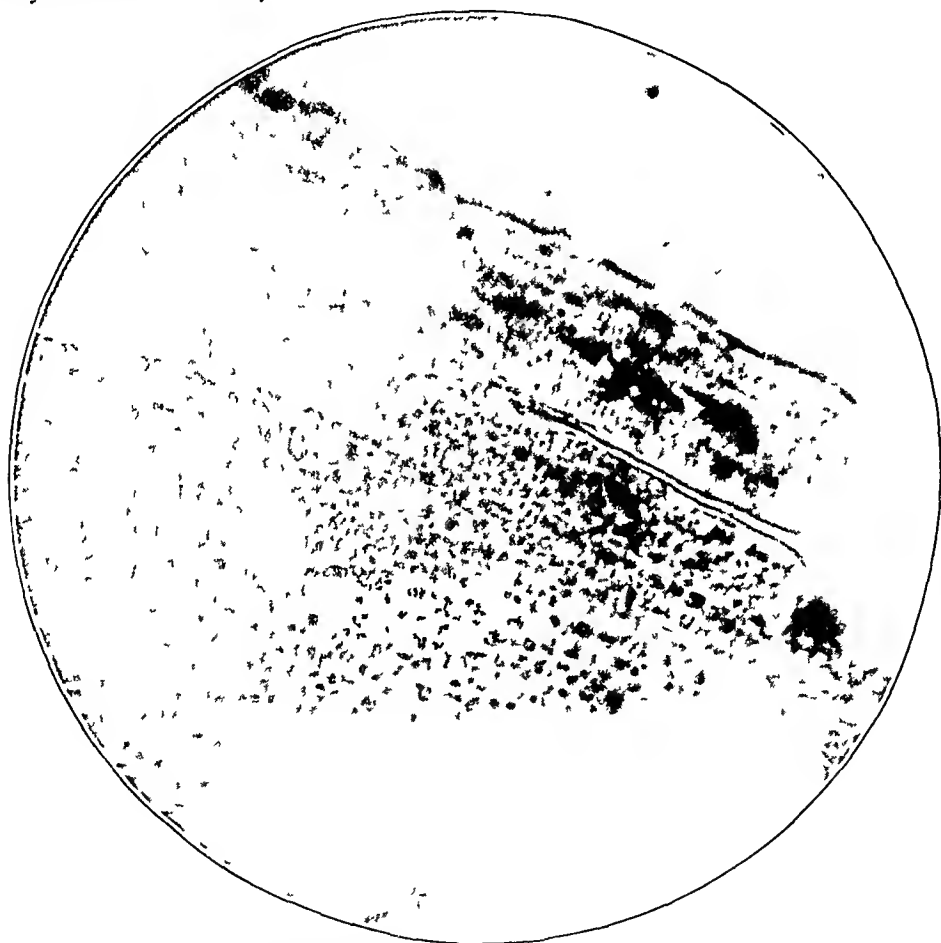


Fig 1—Case A (ventricular septum) scharlach R stain. Carmin red fat droplets (black in microphotograph) in longitudinal rows between the fibrillae of the muscle cell and arranged transversely (on either side of Krause's membrane).

Osler,<sup>5</sup> discussing the anatomic basis of cardiac insufficiency, says, 'Fatty degeneration is a very common condition. It is found in the failing nutrition of old age, of wasting diseases and of cachectic states, in prolonged infectious fevers in which it may follow or accompany the parenchymatous changes. In pernicious anemia and in phosphorus

5 Osler, William. Principles and Practice of Medicine 1918, p 788

poisoning the most extreme degrees are seen. Lastly in the hypertrophied ventricular wall in chronic heart disease fatty change is by no means infrequent. There appears to be a special proneness to fatty degeneration in the heart muscle which may, perhaps, be connected with its incessant activity."

It is our contention that the diagnosis of fatty degeneration of the heart is made too frequently in the pathologic laboratory. Here the criterion of this condition is the presence of fat within the muscle cell. Adam<sup>1</sup> says, "Fatty degeneration of the heart is a common condition characterized by the presence of minute globules of fat in the muscle

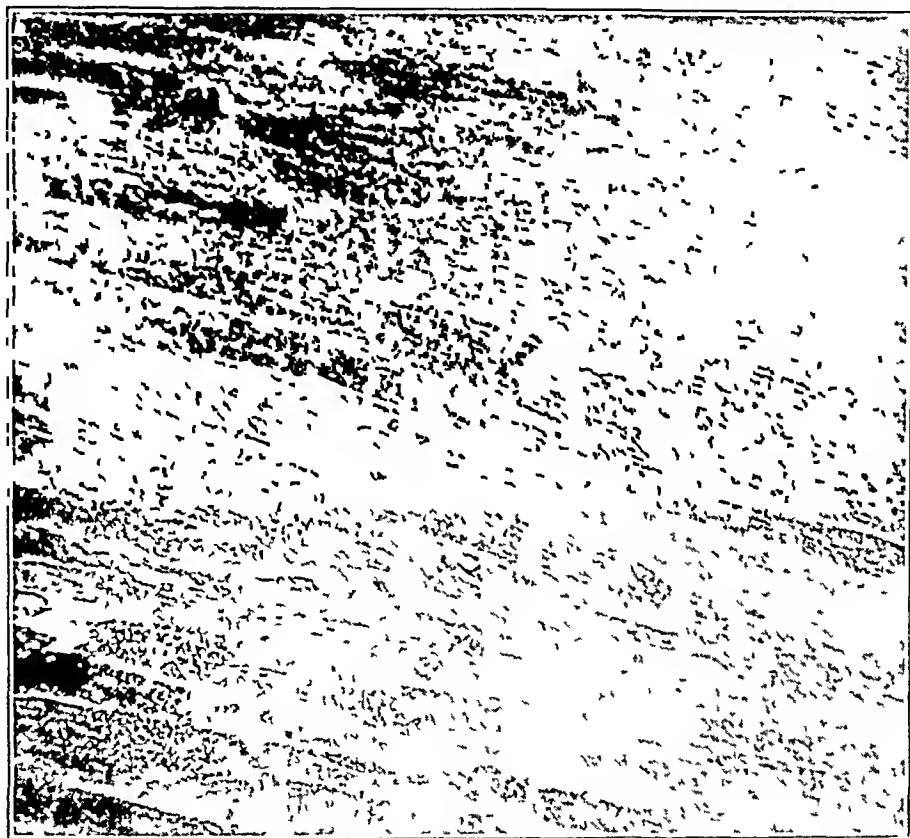


Fig 2—Textbook illustration of fatty degeneration of the heart (From Stengel and Fox Textbook of Pathology, Ed 7, 1921, p 503)

fibers which are deposited in small droplets, generally in the line of the longitudinal fibrillae of the cell." Years ago, then, from the work of Virchow,<sup>6</sup> Adam<sup>7</sup> and others, we have all been taught that visible fat in the cardiac muscle cell is pathologic, i e, fatty degeneration is present.

To prove our stand that fatty degeneration of the heart is diagnosed too often, we decided to examine a series of pathologic hearts and to utilize normal human hearts as controls.

6 Virchow, R. Virchows Arch f path Anat 1 94, 1847

7 Adam<sup>1</sup> Principles of Pathology, Ed 2 11 151 1910

We examined, postmortem, the hearts of twelve patients from the medical services of Dr L A Conner and Dr W L Williams at the New York Hospital. These patients had been in the hospital as "cardiacs," i e, they had myocardial or valvular disease or both, and the symptoms from which they suffered were primarily ascribed to their hearts. They all died with the classical symptoms of myocardial failure. The following is the clinical history typical of any one of these cases. The pathologic findings in regard to presence or absence of fatty degeneration is also typical of all the hearts.

**CASE 1**—Chronic myocarditis. Patient, aged 57, admitted March 3, 1921, and discharged April 25, 1921. Entered hospital with the complaint of dizziness, swelling and pain in abdomen and legs. Gave a long history of alcoholism and for past five years had dyspnea on exertion and precordial pain, rarely fainting attacks.

**Examination**—His heart was enlarged, 13 cm to the left in sixth space and 2 cm to the right in fourth space. Heart sounds were of very poor quality and distant. Extrasystoles and slow rate, from 50 to 60.

Blood pressure 140/90. Urine contained heavy trace of albumin, hyaline and granular casts, specific gravity, 1.020. Blood urea 40 mg per 100 cc.

**Necropsy Findings**—Chronic parenchymatous nephritis, kidney infarcts, general atherosclerosis, chronic myocarditis (replacement fibrosis), hypertrophy of heart, liver congestion, chronic perisplenitis.

The gross examination of the heart showed on the surface of the organ a considerable increase of fatty tissue. The heart was much enlarged. No areas of fibrosis were observed. Valves were negative, except for very slight thickening of the edge of the mitral valve. Coronaries markedly thickened and calcified and narrowed throughout.

The microscopic examination of the heart revealed connective tissue replacement, considerably so in the region of the left apex and in the right ventricle. The septum showed a moderate degree of fibrous infiltration. A few small round cell foci were present at the pericardial surface of the left ventricle, rarely in the muscle itself.

Innumerable fat droplets were found in large quantities in the muscle cells proper. These were arranged in the cell in the classically described positions for fatty degeneration, i e, in longitudinal and transverse rows between the muscle fibrillae, and areas of muscle cells filled with fat alternated with those practically free from this tissue.

Willius<sup>8</sup> correlated the electrocardiographic findings during life with the pathologic condition of the cardiac muscle at death. He describes five cases of heart failure, reporting "marked fatty degeneration" in each case. Any well known textbook of pathology<sup>9</sup> illustrates fatty degeneration of the heart muscle exactly duplicating the pictures we obtained in the hearts of every one of our series of cases. Our scharlach R strain demonstrated the minute red droplets in every heart.

<sup>8</sup> Willius, F A. Mayo Clinic Collected Papers for 1918, p 410.

<sup>9</sup> MacCallum. Textbook of Pathology, 1920, Ed 2 p 84. Beattie and Dickson. Textbook of General Pathology, 1921 pp 40 and 45. Stengel and Fox. Textbook of Pathology, 1921, Ed 7, p 503.

examined. Previously we believed as other writers did that visible fat is pathologic, but when every heart depicted this finding, our opinion was strengthened that this view was incorrect. Hence, we had recourse to our series of controls. This is the crux of the matter. If the normal hearts evidenced no fat droplets in the muscle cell, we could say that

## MICROSCOPICALLY VISIBLE FAT IN NORMAL HUMAN HEART MUSCLE

Case No	Age	Sex*	Color	Cause of Death	State of Nutrition at Necropsy	Presence of Diffuse Red Fat Droplets in the Muscle Cell Between the Fibrilla Arranged in Longitudinal and Transverse Rows	Presence of Golden Brown Pigment at the Poles of the Nuclei, i. e., Pigment of Brown Atrophy
A	33	♂	White	Blackjacked, i. e., skull fracture, died within few hours	Good	Large quantity	Large quantity
B	45	♂	White	Stab wound of heart, died immediately	Good	Slight or moderate amount	Large quantity
C	45	♂	White	Fracture cervical vertebra, died in few hours	Good	Present in some areas	Large, coarse brown, bipolar pigment
D	23	♀	White	Cerebral hemorrhage, died either immediately or within few hours	Very good	Abundance of granules	Good many granules
E	40	♂	White	Fracture of skull, died in 3½ hours	Good	Abundance of granules	Good many granules
F	31	♀	White	Clinical diagnosis not made	Somewhat emaciated	Abundance of granules	Good many granules
G	20	♂	White	Shot to death, died within 1 hour	Good	Very few granules	Good many granules
H	42	♂	White	Acute alcoholism	Good	Moderate amount	Very many granules
I	32	♀	Black	Died in a few hours from hemorrhage after attempted criminal abortion	Good	Moderate amount	Very many granules
J	34	♀	Black	Acute alcoholism	Good	Great many granules	Very many granules
K	56	♂	White	Cerebral hemorrhage from blow	Good	Great many granules	Very many granules
L	15	♂	White	Shot, died instantly	Good	Many granules	Moderate amount
M	8	♂	White	Run over by truck, died in few hours	Good	Many granules	Moderate amount

\* In this column, ♂ denotes male, and ♀ female

this finding was pathologic. However, if the controls showed fat granules in human cardiac muscle to be a common finding then our entire conception of fatty degeneration of the heart would have to be revised, pathologically and clinically, because the latter depended for proof on the necropsy findings.

Hence, we obtained thirteen hearts at the Bellevue Hospital morgue from persons who had met sudden, violent death by bullet or stab wounds, etc., and where the necropsy failed to show any abnormality that was apparent to the unaided eye. These people ranged in age from 8 to 56 years, the average age being 32 years. Sections were taken from each ventricle, septum and auricle. The tissue was fixed in

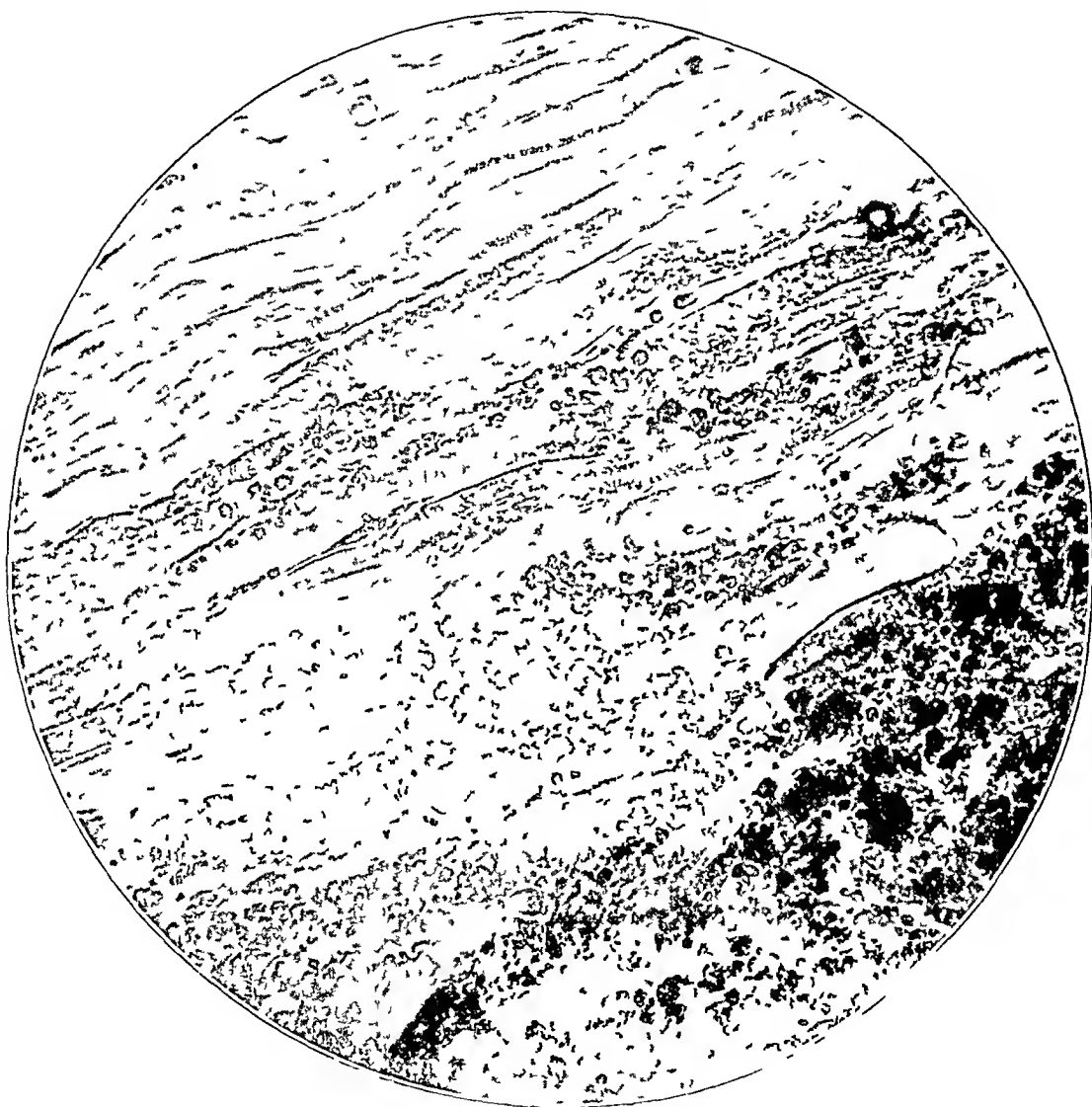


Fig 3—Case 2. Localized area of fatty degeneration in vicinity of infarcted heart muscle. (Low power microphotograph.)

liquor formaldehyd and within twenty-four hours frozen sections were stained with a saturated solution of scharlach R dye in equal parts of 70 per cent alcohol and pure acetone. The technic followed was that given by Mallory and Wright<sup>10</sup>. At the conclusion of the experi-

10 Mallory and Wright. *Histological Technique*, Ed 7, p 167

ments we stained one of the hearts with osmic acid (material treated with formaldehyd, placed in Marchi's fluid and cut by the freezing microtome) The results obtained were similar to those obtained with scharlach R The table and microphotographs show our findings In regard to the scharlach R stain, we found small red dioplets of varying sizes in the sarcoplasm of the cardiac muscle cells These were arranged in longitudinal and transverse rows, the longitudinal dioplets appearing between myofibrillae The number of granules varied Some hearts were stained diffusely and uniformly, some scarcely at all, and

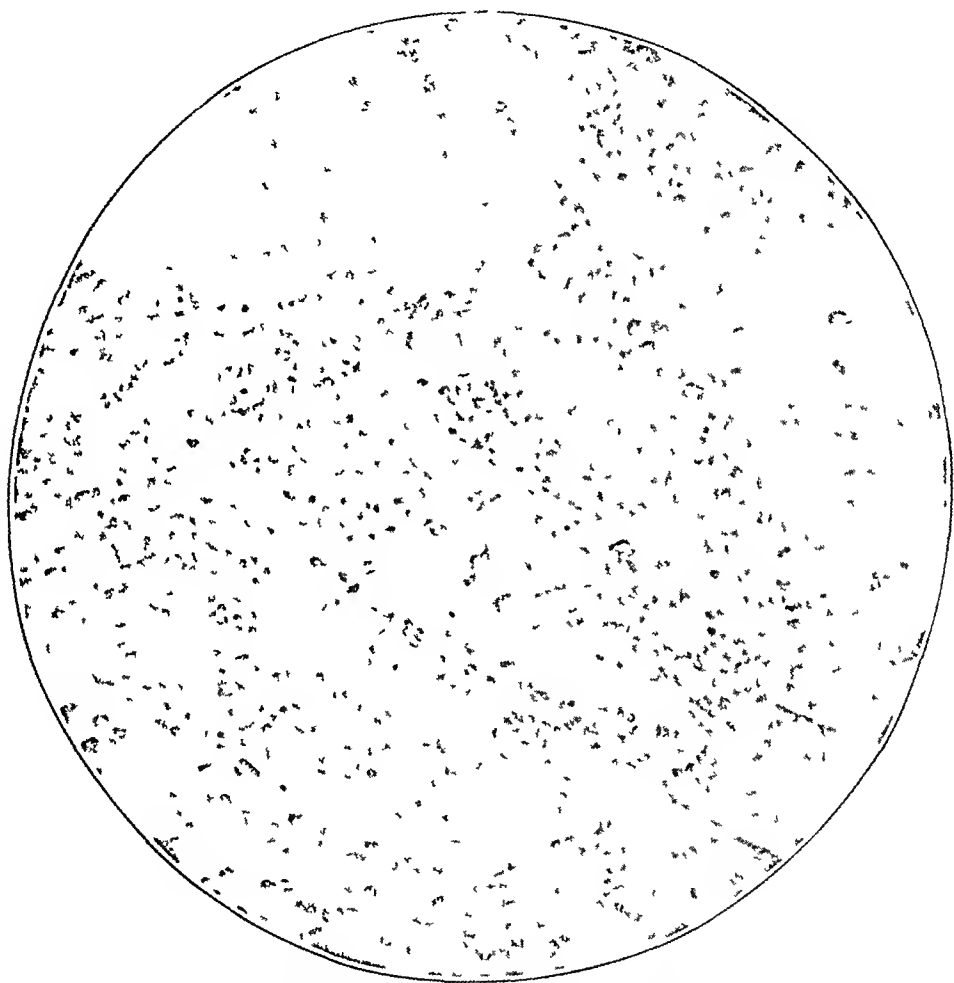


Fig 4—Case D Osmic acid stain Results similar to scharlach R (see Case A, Fig 1)

commonly there were groups of cells which took the stain well while in the immediate vicinity were cells which contained little, if any, fat The findings were similar to those in the diseased hearts

The so-called pigment of brown atrophy, which is located at the poles of the nucleus and is supposed to be an indication of senility of the muscle, was stained yellow, yellow brown or golden brown with scharlach R At first we found it a little difficult to distinguish between it and the diffuse fat droplets, but after some experience we were able,



in practically every case, to differentiate between the coarser brownish bipolar granules and the smaller red fat droplets distributed diffusely throughout the cell and arranged in longitudinal and transverse rows. With osmic acid the bipolar pigment was stained light brown, whereas the fat granules were intensely black.

Hofbauer<sup>11</sup> described visible fat in normal human fetal muscles in 1905. Bell,<sup>12</sup> in 1912, first showed that visible fat is normally present in the cardiac muscle of the common laboratory mammals. He also demonstrated that the quantity of visible fat is increased when fatty foods are given and diminished when the animals are starved. Wegelin<sup>13</sup> found fat in the cardiac tissue of rats. He also examined the heart of an insane man who had jumped out of the window, and found fat in quantities, although the organs appeared to be normal at the necropsy. He expressed the belief that fat could be demonstrated microscopically in normal human heart muscle. Eyselen<sup>14</sup> did not agree with this.

Bullard<sup>15</sup> in 1912 stated that although scharlach R was not specific for neutral fat (scharlach R and sudan III stain neutral fats, fatty acids, soaps and lipoids with varying degrees of intensity), and, although he did not believe that all the colored droplets in mammalian cardiac muscle were neutral fat, yet he thought that most of them undoubtedly were.

In a subsequent communication, Bullard<sup>16</sup> showed that microscopically demonstrable fat is present in the normal cardiac tissue of rats, cats, dogs, hogs, oxen and sheep. More than 200 animals were investigated. The fat droplets in the sarcoplasm were arranged in rows between the muscle fibrillae and in transverse lines in segments on either side of the membrane of Krause. He also noted fatty fibers side by side with nonfatty areas. However, in other cases all the cells showed a uniform diffuse mottled appearance.

We do not wish to go into detail of the histology and chemistry of fats. Those interested can obtain in detail the reason for the conclusion of Bullard. He gave decisive evidence for believing that visible

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11 Hofbauer, J. Die Physiologische Fettinfiltration des Fetalen Herzens, *Anat Anz* **27** 426, 1905.

12 Bell, E. T. The Interstitial Granules in Fatty Metamorphosis of Striated Muscle, *J Path & Bacteriol* **17** 147, 1912.

13 Wegelin, C. Ueber alimentäre Herzmuskelverfettung, *Berl klin Wchnschr* **50** 2125, 2190, 1913.

14 Eyselen, K. Untersuchung über den Fettgehalt der Herzmuskulatur, *Virchows Arch f path Anat* **218** 30, 1914.

15 Bullard, H. H. The Microscopical Demonstration of Fats in Tissue Sections, *J M Research* **27** 55, 1912.

16 Bullard, H. H. On the Occurrence and Physiologic Significance of Fat in the Muscle Fibers of the Normal Myocardium and Atrioventricular System, *Am J Anat* **19** 137, 1916.

droplets of neutral fat occur in physiologic circumstances in the cardiac muscle fibers of mammals. Space prevents the repetition of these arguments and proof.

He utilizes a 20 per cent solution of liquor formaldehyd<sup>17</sup> rendered isotonic with 0.75 gm sodium chloride per hundred cubic centimeters of liquid. Tissues are fixed for from one-half to five hours and then cut on the freezing microtome. If this procedure is followed, the quantity of fat does not differ from that obtained in fresh tissues. By means of Herxheimer's alkaline alcoholic solution of scharlach R, fat may often be demonstrated in larger amounts than by the simple alcoholic solution of dye. This stain<sup>18</sup> is a saturated solution of scharlach R in 70 per cent alcohol to which 2 gm of sodium hydroxide are added for every 100 cc of fluid. Precipitates must be avoided.

Within the last few years several articles<sup>19</sup> have appeared in the literature that tend to prove that the pigment of brown atrophy is an endogenous melanin and that some of the red droplets in the cell brought out by the scharlach R are of exogenous lipochrome. But this lipochrome is stained a deep blue by Nile blue stain, not red, as the fat granules are. Other writers, too, state that the pigment can be separated from the fat.

The presence of fat in the cells of normal human cardiac tissue was a revelation not only to us but to others. An eminent pathologist was shown our scharlach R sections of normal hearts. Without knowing the history of the cases he stated that the hearts were pathologic, i. e., that they showed fatty degeneration. He was surprised to learn that the sections were from normal human hearts.

It must be clear by this time that visible fat is a normal finding in human cardiac muscle. Similarly, it must also be evident that visible fat within the muscle cell does not signify fatty degeneration.

Although we believe that fatty degeneration is quite rare in the hearts of those dying from cardiac disease, localized areas of fatty degeneration in the heart muscle are not so uncommon. One of our twelve pathologic hearts depicted this finding.

CASE 2—Coronary artery disease. Patient aged 59, admitted to New York Hospital May 25, 1921, died June 7, 1921. Sixteen months before entering hospital had severe attack of abdominal gas pains. Recurrences of increasing frequency with dyspnea on exertion. Cough present June 3, 1921. Pulse became irregular. Heart enlarged slightly, sounds distant. Clinically, and from the electrocardiographic point of view patient was considered to have coronary artery disease with thrombus. Blood pressure 110/70. Urine, normal, Wassermann negative.

The gross examination of the heart showed that organ to be enlarged, weighing 500 gm. On the posterior surface of the left ventricle there was a pale focus. Three to four millimeters beneath the endocardium there was a grayish yellow layer. Coronaries showed marked thickening, the lumen of the anterior descending branch of the left coronary was occluded by an old thrombus.

17 Mann, G. *Physiological Histology*, Oxford, Clarendon Press, 1902, p. 88.

18 Herxheimer, G. *Ueber Fettfarbstoffe*, *Deutsch med Wchnschr* **27** 607, 1901.

19 Dolley, D. H., and Guthrie, F. V. *The Pigmentation of Heart Muscle*, *J. M. Research* **42** 289, 1921.

The microscopic examination revealed necrotic areas in the septum. Adjacent portions showed marked fatty degeneration as shown in sections stained with scharlach R. There were areas of fibrous tissue replacement. In the lateral wall of the left ventricle there were also areas of fibrous replacement with less marked but very evident fatty degeneration and infiltration. The right ventricle appeared normal except for a slight increase of connective tissue. Here evidence of necrosis, fibrosis, nuclear changes, disappearance of muscle striations, great numbers of fat granules, etc., helped to make the diagnosis of fatty degeneration of this localized area.

It appears, therefore, that in twelve pathologic hearts in which one might have diagnosed fatty degeneration of more or less severity not one showed this condition. This we proved on the bases of the normal hearts as a standard.

Certain facts must clearly be evident. Normal hearts contain microscopically visible fat. Microscopically visible fat alone does not stamp a heart as demonstrating fatty degeneration. Fatty degeneration of the heart is much less common than supposed. Clinically fatty degeneration of the heart is, therefore, a very uncertain diagnosis.

#### SUMMARY

1 The clinical diagnosis of fatty degeneration of the heart is still made too commonly. It is a very uncertain diagnosis.

2 There are no symptoms peculiar to this condition, nor is there any pathognomonic sign for its diagnosis.

3 The diagnosis should be made by inference only. The etiologic factors in fatty degeneration will help.

4 In reference to degenerative changes in the heart muscle, fatty and fibrous changes should not be differentiated clinically. This is Mackenzie's<sup>20</sup> view.

5 Fatty degeneration of the heart is a finding too frequently made postmortem. The presence of microscopically visible fat in the muscle cell is not sufficient for this diagnosis.

6 In human cardiac muscle microscopically visible fat is normally present, it is by no means necessarily pathological. The fat resides in the sarcoplasm between the muscle fibrils and is arranged in longitudinal and transverse rows. Apparently, the amount has no relation to the state of nutrition at the time of death, neither has the age of the subject (from 8 to 56 years), the color, nor the sex.

7 The picture presented by the diffuse red droplets (scharlach R) or the black granules (osmic acid) closely resemble the classical illustrations many textbooks of pathology utilize to picture fatty degeneration of the heart. True fatty degeneration, e. g., the "tiger-heart," is recognized by the greater number and size of the granules, the evidence of inflammation, e. g., nuclear changes, disappearing of striations, etc.

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20 Mackenzie, J. *Diseases of the Heart*, 1918, Ed. 3, pp. 313-315.

8 In all experimental work in which sections of cardiac tissue are stained for fat, normal conditions should be kept in mind and control studies made whenever possible. In the investigation of twelve pathologic hearts we found not one organ demonstrating fatty degeneration. Another writer performing work similar to ours reported "marked fatty degeneration" in every case.

9 The so-called pigment of brown atrophy of the heart, which is supposed to be an indication of degenerative processes, e. g., senility, was found in moderate amounts in two healthy boys, one 8 years of age, the other 15.

# INTRAPERICARDIAL RUPTURE OF AORTIC ANEURYSM IN A BOY SIXTEEN YEARS OF AGE \*

DE WAYNE G RICHEY  
PITTSBURGH

Aneurysm of the thoracic aorta in the young is not encountered frequently After a rather detailed search, it has been possible to collect from the literature forty-one instances of aneurysm of the thoracic aorta in persons not more than 18 years of age We could not find a record of an earlier case than that reported in 1834 by R T Smith,<sup>1</sup> who described an aneurysm of the ascending aorta in a boy, aged 16 The aneurysm had ruptured into the pericardial sac while the lad was ascending a ladder Since then sporadic case reports have appeared and tabulations of known cases have been made by Le Boutillier,<sup>2</sup> Bronson and Sutherland,<sup>3</sup> Heiman <sup>4</sup> and Calvin <sup>5</sup>

As the accompanying table will show, twenty-four of the forty-one recorded cases were in males The ages ranged from 15 to 18 years Less than half (nineteen) had been amplified by necropsy Nineteen had involved the ascending limb of the aortic arch, two the ascending and transverse portions, two the transverse part alone and two the descending limb In the remaining cases it was stated that the aneurysm occurred along the arch Fifteen had ruptured, at least eight of which had broken into the pericardial sac

In four, those of Roger,<sup>6</sup> Ric,<sup>7</sup> F J Smith<sup>8</sup> and Madsen<sup>9</sup> no cause had been ascribed to the production of the aneurysm It is worthy of note that nearly half of all the cases (twenty) were associated with a mycosis, usually rheumatic fever, with or without an acute, sub-

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\*Read before the American and Canadian Sections, International Association of Medical Museums, Washington, D C, May, 1922

1 Smith, R T Lancet **1** 626, 1834

2 Le Boutillier Am J M Sc **125** 778, 1903

3 Bronson and Sutherland Brit J Child Dis **15** 16, 1918

4 Heiman Arch Pediat **36** 543, 1919

5 Calvin, J K Aneurysms of the Thoracic Aorta in Children, Am J Dis Child **21** 327 (April) 1921

6 Roger Bull et mem Soc med d hôp de Par, p 499, 1863

7 Ric Wien med Wchnschr **39** 556, 1889

8 Smith, F J Tr Path Soc Lond **48** 53, 1897

9 Madsen Med Rec, Bergen, **28** 530, 1916

acute or chronic bacterial endocarditis. These cases had been described by R. T. Smith,<sup>1</sup> Moutard-Martin,<sup>10</sup> Thibierge,<sup>11</sup> Moore,<sup>12</sup> Sanné,<sup>13</sup> A. A. Smith,<sup>14</sup> Bacelli,<sup>15</sup> Murdock and Welch,<sup>16</sup> Le Boutilier,<sup>2</sup> Jordan,<sup>17</sup> Feytaud,<sup>18</sup> Roy,<sup>19</sup> Klotz,<sup>20</sup> Miguel,<sup>21</sup> and Calvin,<sup>5</sup> while Oppenheimer's<sup>22</sup> case showed atheromatous plaques in the media. It is equally noteworthy that only two cases—those of Willson and Marcy,<sup>23</sup> and Heiman,<sup>4</sup> presented irrefutable evidence of syphilis, despite the fact that virtually every author gave cognizance to syphilis as a probable etiologic factor. Trauma seemed to play a part in two instances (Pendin,<sup>24</sup> MacKeen<sup>25</sup>) and two cases occurred in athletes during violent exercise (Jones,<sup>26</sup> Berry<sup>27</sup>). In four cases—those of Hutchinson,<sup>28</sup> Willett<sup>29</sup> and Clarke—the aneurysm was due, apparently, to erosion of the aortic wall by a contiguous suppurating or tuberculous focus.

It has long been assumed by many that inasmuch as syphilis plays a leading rôle in the causation of aortic aneurysms in adults, it must necessarily follow that the *Spirocheta pallida* is the offender in similar lesions in the young. At the same time, the importance of lesions produced in the arterial tree during acute rheumatic fever, recurrent rheumatic fever or chronic rheumatism, in the presence or absence of a bacterial endocarditis, has been underestimated, as Feytaud<sup>18</sup> and Klotz<sup>20</sup> have indicated. Moreover, we admit that the young are especially susceptible to infection by the *Streptococcus viridans* group of organisms, but as our attention has been centered more particularly on the portals of entry, the endocarditides and arthritides, we have forgotten that the vascular tree is also prone to involvement by similar inflammatory processes, the end result of which is not infrequently aneurysm, with or without rupture. It is only natural, therefore, that

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10 Moutard-Martin. Bull. de la Soc. Anat. 1875, p. 775

11 Thibierge. La France méd. 2, 913, 1881

12 Moore. Tr. Path. Soc. Lond. 34, 71, 1882

13 Sanné. Rev. mens. d. mal. de l'enf. 5, 56, 1887

14 Smith, A. A. Med. Rec. 44, 349, 1893

15 Bacelli. Semaine med. 18, 137, 1898

16 Murdock and Welch. Edinburgh Hosp. Rep. 6, 84, 1900

17 Jordan. Lancet. 1, 515, 1903

18 Feytaud. These de Paris, 1906

19 Roy. Bull. et mem. Soc. Anat. de Par. 28, 198, 1908

20 Klotz. J. Path. & Bacteriol. 18, 259, 1913

21 Miguel. Bull. gén. de Therap. 9, 393, 1919

22 Oppenheimer. Virchows Arch. f. path. Anat. 181, 382, 1905

23 Willson and Marcy. Proc. Path. Soc. Phila. 16, 63, 1914

24 Pendin. St. Petersburg med. Wchnschr. 7, 195, 1890

25 MacKeen. Med. News. 61, 272, 1892

26 Jones. After Crisp, Diseases of Blood Vessels, 1847, p. 341

27 Berry. Brit. M. J. 2, 1745, 1898

28 Hutchinson. Tr. Path. Soc. Lond. 5, 104, 1854

29 Willett. Tr. Path. Soc. Lond. 43, 38, 1892

the streptococcal group, in the presence or absence of the syndrome recognized as rheumatic fever and its sequels, is the predominant causal factor in the production of aneurysms in the young, and that syphilis, evidently, plays a minor rôle. Certainly, the facts as presented in these collected cases confirm these views.

COLLECTED CASES OF ANEURYSM OF THORACIC AORTA IN PERSONS LESS THAN EIGHTEEN YEARS OF AGE

Author	Year	Sex*	Age	Necropsy	Location	Rupture	Associated with
R T Smith	1834	♂	16	Yes	Ascending	Intrapericardial	Chronic endocarditis and exertion
Jones	1847	♂	16	Yes	Ascending	Intrapericardial	Exertion, athlete (?status lymphaticus)
Hutchinson	1854	♀	4	Yes	Arch	Yes	Erosion of thoracic abscess
Roger	1863	♀	10	No	Arch	No	Unknown
Moutard-Mar tin	1865	♂	2	Yes	Ascending	No	Subacute endocarditis and congenital heart disease
Thubierge	1881	♀	17	Yes	Ascending	No	Subacute endocarditis
Moore	1882	♀	5	Yes	Ascending	No	Acute endocarditis
Sanne	1887	♂	13	Yes	Ascending	No	Acute endocarditis
Rie	1889	♂	5	No	Arch	No	Unknown
Pendin	1890	♀	12	No	Arch	No	Trauma, fall
Willett	1892	♂	4	No	Descending	Yes	Erosion by suppurating lymph node
MacKeen	1892	♀	5	No	Arch	No	Trauma, fall
A A Smith	1893	♂	18	No	Ascending and transverse	No	Acute rheumatic fever
Smith and Targett	1897	♂	9	Yes	Transverse	No	Congenital stenosis
F J Smith	1897	♂	9	No	Descending	No	Unknown
Berry	1898	♂	15	Yes	Ascending	Intrapericardial	Exertion athlete (?status lymphaticus)
Brace	1898	♂	16	No	Arch	No	Acute rheumatic fever
Murdoch and Welch	1900	♂	12	Yes	Ascending	No	Acute endocarditis and congenital heart disease
LeBoutillier	1903	♀	9	No	Transverse	No	Acute rheumatic fever and pertussis
Jordan	1903	♂	6	Yes	Ascending	Intrapericardial	Septic aortitis, embolism of the coronary vasorum
Wasajima	1903	♂	13	Yes	Ascending	Intrapericardial	Congenital stenosis
Oppenheimer	1905	♀	9	Yes	Arch	Yes	Atheromatous plaques in media
Feytaud	1906		12-16	No	Ascending	No	Acute rheumatic fever
Feytaud	1906		12-16	No	Ascending	No	Acute rheumatic fever
Feytaud	1906		12-16	No	Ascending	No	Acute rheumatic fever
Feytaud	1906		12-16	No	Ascending	No	Acute rheumatic fever
Feytaud	1906		12-16	No	Ascending	Yes	Acute rheumatic fever
Willson and Marey	1907	♂	4	Yes	Ascending and transverse	Intrapericardial	Syphilis
Horder	1907	♂	12	Yes	Ascending	Intrapericardial	Congenital stenosis of aorta
Roy	1908	♂	15	Yes	Ascending	No	Acute infection of unknown character
MacNalty	1909	♂	14	No	Arch	No	Congenital hare lip etc
Armitage	1909	♂	7	No	Arch		(?status lymphaticus)
Klotz	1913	♂	6	Yes	Ascending	No	Congenital cardiac anomaly
Madsen	1916	♂	1½	Yes	Arch	Yes	Acute mycosis, vegetative mitral endocarditis
Bronson and Sutherland	1918	♂	4	Yes	Ascending	Intrapericardial	Not mentioned
Heiman	1919	♂	13	No	Arch	No	Congenital stenosis
Miguel	1919	♂	14	No	Arch	No	Syphilis
Calvin	1921	♂	11	No	Arch	No	Acute infection of unknown character
Calvin	1921	♂	9	No	Arch	No	Recurrent rheumatic fever
Clarke†					Arch	Yes	Recurrent chorea
Clarke†					Arch	Yes	Erosion by caseous lymph node
Clarke†					Arch	Yes	Erosion by caseous lymph node

\* In this column, ♂ indicates male and ♀ female

† Quoted by Calvin

Four of the cases, as delineated by Smith and Targett,<sup>30</sup> Wasajerna,<sup>31</sup> Horder<sup>32</sup> and Bionson and Sutherland,<sup>3</sup> were associated with a stenosis of the aorta in the vicinity of the ductus arteriosus. The stenosis varied from a coarctation to narrowing of a lesser degree. Armitage's<sup>33</sup> case was attended by a congenital heart lesion. There can be no doubt that a certain number of aortic aneurysms in the young occur proximally to a congenital stenosis of the aorta, where, apparently, they depend on mechanical factors for their production, just as spontaneous rupture of the aorta in the absence of distal constriction can come to pass, as described by Osler<sup>34</sup> in a boy aged 13 years.

In the case I report, there was no evidence of syphilis or mycosis. No coarctation of the aorta could be found, but there was a uniform narrowing of the aortic arch just beyond the aneurysm of the ascending limb, which I regard as a hypoplasia associated with status thymico-lymphaticus. As I have been unable to unearth a similar case in the literature, the findings are detailed herewith.

#### REPORT OF CASE

*History*—A boy, aged 16 years, died suddenly as a result of a hemopericardium following the rupture of an aneurysm of the ascending limb of the aortic arch into the pericardial sac. Clinically, the case has virtually no status, as the youth was found dead, coming to necropsy on my service as pathologist to the coroner. It was known that, in the performance of his duties, he had been ascending and descending a ladder. At a later date it was learned from his parents that he had always been a healthy, active child, fond of play and interested in his school work. His birth had been uneventful. Early in life the mother noted a slight tendency to clubbed feet, a relaxation of the inguinal rings and a slight difficulty in articulation—due to tongue-tiedness. Although he played out of doors frequently, he had always been pale. Six years before death, he fractured his arm by a fall while playing. He had not had diphtheria, scarlet fever, tonsillitis, rheumatism, whooping cough or any of the diseases of childhood, save measles. The mother and father had always been well. Their blood yielded a negative Wassermann reaction. Three children were living and well. One other had died of scarlet fever.

*Necropsy Report*—The body had a cream colored pallor. The skin was soft, lusterless and delicate in texture. There was no axillary hair. The escutcheon was scant and tended to the female type. The superficial veins of the chest and abdomen were distended. The thymus was enlarged, weighing 60 gm., but nothing but hyperplasia could be demonstrated in it microscopically. The mediastinal and mesenteric lymph nodes were also hyperplastic, but otherwise healthy. There were 100 cc. of clear, watery fluid in the abdominal cavity. The liver and spleen gave evidence of chronic passive congestion. All the arteries were small and thin walled. The ascitic fluid yielded a negative Wassermann reaction.

30 Smith and Targett. *Tr. Path. Soc. Lond.* **48** 53, 1897.

31 Wasajerna. *Ztschr. f. klin. Med.* **90** 405, 1903.

32 Horder. *St. Bartholomew's Hosp. Rep.* **43** 57, 1908.

33 Armitage. Quoted by McGraw, *Tr. Am. Surg. Assn.* **27** 532, 1909.

34 Osler. *Osler's Modern Med.* **4** 467, 1908.



There was 600 c c of recently clotted blood in the distended pericardial sac. The heart weighed 245 gm, being somewhat larger than the normal heart at this age, due to a moderate hypertrophy of the left ventricle. Otherwise the heart was normal. There was a saccular aneurysm of the ascending portion of the aorta which had caused a relative dilatation of the otherwise normal aortic valve. The aneurysm was directed posteriorly, where on the left lateral wall at a point 2.5 cm above the level of the aortic valve, a linear slit, 1 cm in length, indicated the site of rupture, affording a point of egress for the blood into the pericardial sac. Here the aneurysmal wall was especially thin. On the intimal aspect, two distinct lesions were noted. One (an old, healed rip of the intima) began above the right posterior cusp of the aortic valve and extended transversely on the posterior aortic wall for a distance of 5.5 cm. Due to the process of repair, the wall at this area was thickened. Here, also, the overhanging, rounded edge indicated a beginning dissecting aneurysm which had spontaneously terminated and healed. The other lesion was a more recent one, consisting of a fresh rip in the intima and inner part of the media. This commenced at the left angle of the old tear, extending downward and



Fig 1—External view of aneurysm (reconstructed). The site of intrapericardial rupture is shown at A and the diminutive calibre of aorta at B.

backward to end 5 mm above the left posterior cusp of the aortic valve. That this rent was also dissecting was shown by the fact that the sharp, thin, knife-like edges were undimmed. It was apparent, too, that the tear in the intima had preceded the rupture externally as indicated by the presence of organizing thrombus between the split layers of the media. It was this rip which had led to the intrapericardial rupture, the hemopericardium and the sudden death. Above the aneurysm the aorta was of small calibre, 1.5 cm in diameter, as compared to the normal diameter of 3.2 cm, as given by Vierordt and Schücler<sup>2</sup> for young men between 15 and 25 and by Thoma<sup>3</sup> between 19 and 21. The diameter of the entire aorta was about half the norm, there being no localized stenosis or coarctation. The aorta away from the aneurysm was thin walled (0.75 mm), but otherwise healthy.

*Microscopically*, there was a replacement fibrosis at the site of the old rupture, where considerable fragmentation of the muscle layer had occurred. Only a few scattered lymphocytes and plasma cells were seen. As shown by various

stains, the elastic fibrils were few in number. The other portion of the aortic wall was thin and free from demonstrable inflammatory cell infiltration. No spirochetes could be demonstrated in the aortic wall or heart muscle by the silver stains as described by Warthin and Starry,<sup>36</sup> Haythorn<sup>37</sup> and Levaditi.<sup>38</sup> There was no evidence of fatty degeneration. The kidneys were free from demonstrable inflammatory foci.

*Comment*—There are two outstanding conditions in the specimen. One, the uniform narrowing of the aortic lumen with a marked hypoplastic state of the aortic wall, associated, presumably, with the status thymicolymphaticus and the other that the lesions at the site of the aneurysmal dilatation indicate an old and new rip in the intima. The

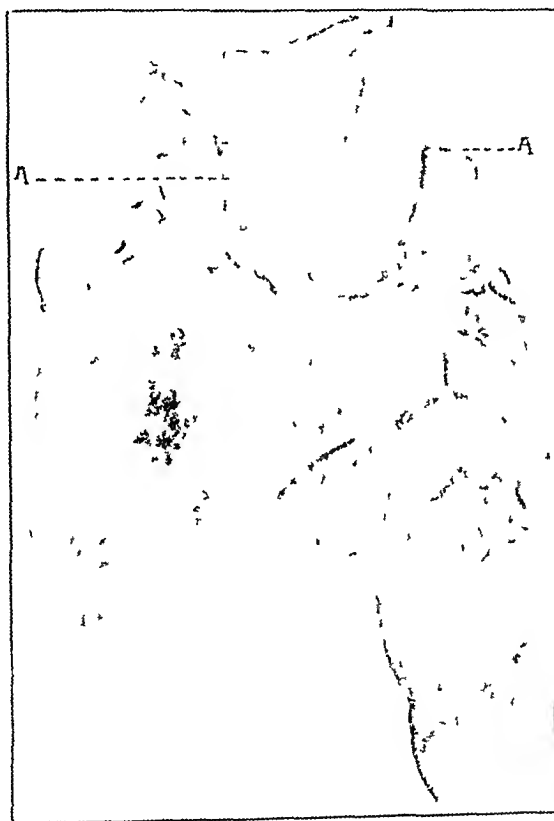


Fig. 2—Internal view of aneurysm. The character of the old, healed intimal rip is shown at A—A'.

old rip evidently had been arrested and healed, while the new one ruptured into the pericardial cavity. It is possible that the old tear occurred six years ago as a result of the fall which fractured an arm and

36 Warthin, A. S., and Starry, A. C. Second Improved Method for the Demonstration of *Spirochaeta Pallida* in the Tissues, *J. A. M. A.* **76**: 234 (Jan. 22) 1921.

37 Haythorn, S. R. A Short Silver Impregnation Method for the Demonstration of *Spirochaeta Pallida* in Tissue, *J. A. M. A.* **76**: 725 (March 12) 1921.

38 Levaditi, Mallory and Wright. *Pathological Technique*, 1908, p. 419.

that the rupture occurred while the boy was climbing up and down the ladder (as in Smith's<sup>1</sup> case) or while straining during the act of defecation

Besides the absence of demonstrable infection, there are certain characteristics common to these aneurysms, as seen in persons under 20, which result from congenital malformations of the aorta. Naturally, they occur proximally to the point of narrowing, most frequently involving the ascending limb of the aortic arch. Almost invariably they are found on the convexity of the ascending aorta, in that region which stands the brunt of the blood current. The aneurysm is fusiform

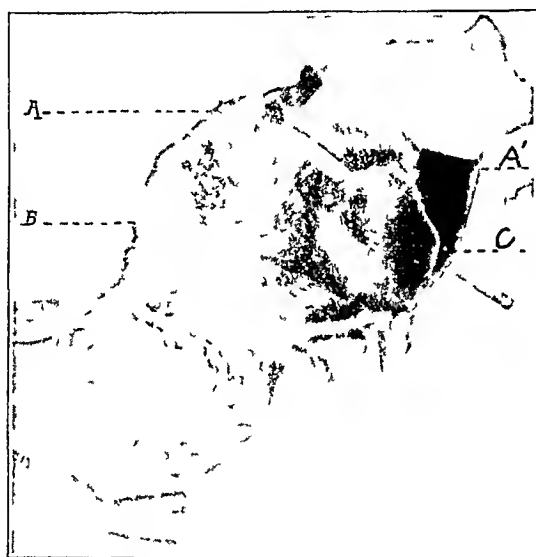


Fig 3—Internal view of aneurysm. The old rip is again seen at A—A' and the new one which led to the fatal rupture as indicated by the inserted match stem, at B. At C can be seen the undermined edge of the healed rip, showing the tendency of the lesion to dissect.

or saccular, and not uncommonly there is a sharp, well defined rip in the intima and inner layers of the media with a beginning dissecting aneurysm, terminating in rupture into the pericardial sac, the rent in the adventitia rarely being directly opposite that in the intima. All of these properties are embodied in the specimen presented. From the description of their cases, it is altogether likely that the aneurysm recorded by Jones,<sup>26</sup> Berry<sup>27</sup> and MacNalty<sup>39</sup> were dependent, in part, on arterial defects due to status lymphaticus.

Hypoplasia of the cardiovascular system is sometimes associated with lymphatism, although the extensive investigations of Abbott,<sup>35</sup>

Ewing,<sup>40</sup> von Neusser,<sup>41</sup> and Warthin<sup>42</sup> indicate that it is not often a factor in the production of aortic aneurysm. Symmers<sup>43</sup> believes that the increased elasticity of the aortic wall adequately compensates for the mural thinness, although he confirms Norris'<sup>43</sup> observation that rupture of cerebral vessels in the young are occasionally found in subjects with status lymphaticus. Only one reference to aneurysm in a hypoplastic aorta was encountered. Lee Dickinson<sup>44</sup> described two such cases in a man and a woman, aged 29 and 36 years, respectively. Both, however, occurred in the abdominal aorta. Von Neusser<sup>41</sup> and Libman<sup>45</sup> mention the possibility of rips occurring in the intima of a congenitally weak aortic arch, the latter thinker emphasizing the importance of moderate degrees of aortic stenosis in the production of aneurysmal dilatation and cardiac hypertrophy.

I agree with Klotz,<sup>46</sup> unreservedly, that "the mechanical theory of aneurysm which placed greater stress for the production of aneurysm on the effect of high blood pressure or, as others would have it, on the effect of velocity of currents, than on the disease in the wall of the artery had for a time enticed our attention into channels of thought and theory no longer tenable with the newer studies," and, as has been pointed out, no one will gainsay that the vast majority of aortic aneurysms do result after weakening of the wall by bacterial invasion, for "it is only a weakened vessel which can develop aneurysm." It has been demonstrated that purely mechanical aneurysms can be produced usually, in a vessel inherently weak as a result of congenital malformation so that the vessel is unable to withstand a sudden, severe, albeit very transient, rise of blood pressure.

*Summary*—Accordingly, it is my impression from the evidence presented, that this aneurysm followed the old, intimal tear which later healed, that this tear resulted from a sudden increase in arterial tension, forcing the blood through the narrowed aorta, that the hypoplasia, associated with the status lymphaticus, was a contributing cause, that the recent tear also occurred as a result of a sudden increase in blood pressure and that, a short time later, before the new rip had an opportunity to reinforce itself, another strain caused the external rupture with the fatal hemopericardium. Cases very similar to this one have been detailed by Bronson and Sutherland,<sup>3</sup> Horde,<sup>32</sup> Smith and

40 Ewing, James. Military Aspect of Status Lymphaticus. J. A. M. A. **71** 1525 (Nov. 9) 1918.

41 von Neusser. *Augewahltes der klinischer Symptomatologie und Diagnose*, Wien, 1911, p. 197.

42 Warthin. *Arch. Pediat.* **26** 617, 1909.

43 Symmers. *Am. J. M. Sc.* **156** 40, 1918.

44 Dickinson. *Tr. Path. Soc. Lond.* **45** 52, 1894.

45 Libman, E. Personal communication.

46 Klotz. *Am. J. M. Sc.* **155** 92, 1918.

Targett,<sup>30</sup> and Wassajerna,<sup>31</sup> as occurring in the young, and in her observations on congenital stenosis of the aorta, Abbott<sup>35</sup> cites twelve cases of rupture, seven occurring in the ascending limb and five at the site of stenosis, as well as nine cases of aneurysm of the arch, five of which were of the dissecting form

I feel that the case merits attention not merely because of its rarity but as a text to direct attention to the recognition of aortic aneurysms in the young as a potential cause of death, even in the absence of syphilis or other infections, notably rheumatic fever

# BLOOD SUGAR STANDARDS

## PART I NORMAL AND DIABETIC PERSONS

HORACE GRAY, M D

BOSTON

*The Problem*—Carbohydrate tolerance may be studied in terms of either glycosuria or glycemia. Testing the urine for sugar is still of value for physicians who have small opportunity to take blood, as in insurance work, or to have the blood analyzed, owing to remoteness from a laboratory. Blood sugar determinations, on the other hand, have proved more illuminating, especially in diagnosis, and, therefore, in this paper will be considered with little regard for the urine findings or the blood sugar threshold.

Standards should be founded not only on careful examination of a few persons but also on statistical analysis of many persons. Series of more than ten normals seem to have been reported from only six clinics, and of these only two have been of satisfactory statistical size, namely, fifty-three described by Goto and Kuno<sup>1</sup> and fifty-eight by Cummings and Piness.<sup>2</sup>

The opinions resulting from such limited evidence disagree notably. Even the same clinic, and that one of the foremost, has uttered such confusing statements as the following: "Experience by no means justifies the suspicion of diabetes in persons showing figures

0.19 and 0.20 per cent when the subsequent samples are normal"<sup>3</sup> And, on the other hand, "The plasma sugar after a mixed meal, 156 mg, showed the diabetic character"<sup>4</sup>

The apparent arbitrariness of some standards, accordingly, makes necessary, what the quantity of evidence now published makes possible, a critical review. The present performance of this, mainly by consolidating results from all kinds of sources, is admitted to be inherently defective. This fusion, nevertheless, affords a standard more broadly based than any yet available. To supplant this tentative standard we need (1) a large series of normals more carefully chosen than has usually been the case, (2) agreement on the test substance and dose,

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1 Goto, K., and Kuno, N. Studies on Renal Threshold for Glucose, *Arch Int Med* **27** 224 (Feb.) 1921

2 Cummings, R., and Piness, G. A Study of Blood Sugar. A Comparison of the Tolerance for Glucose in Diabetic and Normal Subjects, *Arch Int Med* **19** 777 (May) 1917

3 Allen, F. M., and Mitchell, J. W. A Case of Hereditary Diabetes, *Arch Int Med* **25** 648 (June) 1920

4 Sherrill, J. W. A Case of Hereditary Diabetes, *J A M A* **77** 1779 (Dec. 3) 1921

(3) a minimum fasting interval, or a uniform time after a fixed preceding meal, (4) consistent use of whole blood (or plasma), (5) a constant chemical technic, (6) the same technician, (7) particular attention to psychic hyperglycemia by accepting with caution values obtained from inexperienced subjects or from the more painful punctures, such as the finger tips

*Definitions*—The term blood sugar curve is here applied to any glycemic reaction obtained in a tolerance test (i e, inner tolerance, irrespective of glycosuria or outer tolerance) whether there was record of only one blood sugar figure, or whether there was record of the usual four or five figures fasting, half hour, one hour, two hours and three hours This usage incidentally accounts for the variation in the number of totals in the five different columns in many of the tables

The average represents the arithmetic mean (*M*) of all the values at any one period (e g, fasting, half hour, etc) for any group (e g, of normal and diabetic patients, etc) or combined groups These averages are believed to represent, as nearly as warranted by the facts available, the composite or typical curves to be expected after any given load

The term acme or peak as used throughout this paper signifies the highest blood sugar in any given curve

The term maximum is used in this paper for the highest value in any given group of curves (e g, normal patients with 100 gm glucose, diabetic suspects with 50 gm starch, etc)

The term load covers jointly any test substance (glucose, starch, mixed meal) and any dosage (100 gm carbohydrate, or 50 gm carbohydrate—3 gm protein—0 gm fat, etc)

The glycemic coefficient of Baudouin<sup>5</sup> has not been considered here, owing to the evidence given by Frank<sup>6</sup> and by Bergsma<sup>7</sup> showing the error of the claim that because the usual rise from 0.10 before to 0.16 after a load is only a 60 per cent increase it is safe to consider as normal any 60 per cent rise for example, from 0.20 before to 0.32 after the load

*Number and Grouping of Curves*—In the course of a rather careful search of the literature, more than nine hundred curves have been collected After exclusion of a considerable number, because of some unusual peculiarity of procedure, the remaining curves were sorted into the groups which are summarized in Table 1 and then discussed seriatim

<sup>5</sup> Baudouin, A. Etude sur quelques glycemies, la glycemie experimentale, These, Paris, Dec 24, 1908

<sup>6</sup> Frank, E. Ztschr f physiol Chem **70** 291 (Jan 30) 1911

<sup>7</sup> Bergsma, E. Ztschr f Geburtsh u Gynak **72** 105, 1912

TABLE 1—GROUPS OF CURVES STUDIED

Diagnosis	Part I	Number of Cases
Clinically normal		479
Diabetes mellitus		131
Diabetes with apparently essential hypertension		7
	Part II	
Essential (?) hypertension without diabetes mellitus		36
Nephritis without hypertension and without diabetes mellitus		11
Chronic nephritis and renal glycosuria		3
Renal glycosuria alone		70
Renal glycosuria advancing into diabetes mellitus		1
Diabetes receding (?) into renal glycosuria		3
Pregnancy		69
Puerperium		16
Thyroid disease		75
Hepatic disease		51
Pituitary disease		16
Total		971

## CURVES IN THE CLINICALLY NORMAL

*Fasting Blood Sugar*—The entire series of curves in normal persons can be consolidated fairly only as regards the fasting determinations. Of 431 such, the average was 0.09 per cent, and the most frequent value was 0.10 per cent, the minimum 0.04 per cent, the maximum 0.16 per cent, and the frequency distribution as shown in Table 2.

TABLE 2—FASTING BLOOD SUGAR IN 431 PERSONS CLINICALLY NORMAL

B. S.	0.04	0.05	0.06	0.07	0.08	0.09	0.10	0.11	0.12	0.13	0.14	0.15	0.16
No.	2	6	22	31	59	97	116	66	19	8	0	1	1 = 431

TABLE 3—FREQUENCY OF USAGE OF DIFFERENT TEST LOADS IN NORMAL PERSONS

Load, Gm	Number of Curves
70-100 glucose	300
Mixed meal	57
50-100 cane sugar	26
50 glucose	21
70-100 starch	19
20-25 glucose	16
150-200 glucose	16
100 levulose	13
10-75 fat	7
50 starch	1
Total	479

Exception will be taken immediately to the inclusion as normals of the persons who yielded the fasting findings 0.16 and 0.15 per cent, respectively, probably also the eight subjects with 0.13 per cent, and possibly also the nineteen subjects with 0.12 per cent. Although these findings do not suit our preformed fancy we cannot agree with their peremptory rejection in the following statement, though it appears in one of the most valuable contributions to this subject:

"We are unwilling to allow that Jacobsen's figures be accepted as the standard for normals. It is generally conceded that normal persons



do not have sugar in the urine after the ingestion of 100 gm glucose, even when the glucose is taken into a fasting stomach. Undoubtedly most of Jacobsen's subjects had a somewhat lowered carbohydrate tolerance. Our results, as well as those obtained by Hopkins, support this contention."<sup>8</sup> It is true, that suspiciously high fasting values were reported by Jacobsen,<sup>9</sup> but the objection loses force when we notice the similar high values reported by others. Furthermore, if, in fact, it be "generally conceded, etc.," then general concession is an insecure argument, in the face of the observations from many sources compiled for

TABLE 4—ONE HUNDRED GRAMS GLUCOSE IN PERSONS CLINICALLY NORMAL

Percentage	Number of Observations at Each Hour				
	Fasting	½ Hour	1 Hour	2 Hours	3 Hours
0.03				1	
0.04	2		1		1
0.05	7		1	1	1
0.06	22	1	7	12	2
0.07	27	2	16	21	17
0.08	36	3	18	17	21
0.09	59	3	31	41	19
0.10	63	3	38	43	17
0.11	58	10	34	33	9
0.12	14	23	36	30	7
0.13	6	14	31	16	4
0.14		31	21	13	4
0.15	1	18	14	6	
0.16	1	18	14	16	
<hr/>					
0.17		7	11		1
0.18		6	4		
0.19		13	6		
0.20		1	6	1	
0.21		2	4		
0.22		2	2		
0.23		1	2		
0.24			2		
0.25					
0.26				1	
0.27					
0.28			1		
<hr/>					
Total number	276	158	300	253	103
Percentage of total number to be 0.17 per cent or more	0	20	13	1	1
Mean blood sugar	0.09	0.14	0.12	0.11	0.09
Mode*	0.10	0.14	0.10	0.10	0.08
Minimum	0.04	0.06	0.04	0.03	0.04
Maximum	0.16	0.23	0.28	0.26	0.17

\* The mode is the fashionable or commonest value, by some considered the most typical

Table 4. Out of those 129 curves in normal persons after the ingestion of 100 gm glucose accompanied by urine tests glycosuria was present in 40 per cent, and would probably have been found in an even larger fraction except that in many cases the urine was examined only at one period of the glycemic curve.

*Glucose, 100 Gm, in Normal Persons*—The relative popularity of various loads may be judged from Table 3. The commonest was 100 gm glucose, and this is, therefore, analyzed in detail in Table 4. It was

<sup>8</sup> Hamman, L., and Hirschman, I. I. Studies on Blood Sugar, Arch Int Med 20:761 (Nov.) 1917.

<sup>9</sup> Jacobsen, A. T. B. Biochem Ztschr 56:471, 1913.

considered permissible to include a certain number of curves with somewhat smaller doses, down to 70 gm, inasmuch as these curves were, in general, fully as high as after the full dose of 100 gm. The most interesting rows of figures are the composite means and the maximums and these are therefore also pictured in Chart 1. The salient features are these

1 The average curve of this, the largest published series, is rather lower than has usually been stated, the average peak being only 0.14 per cent

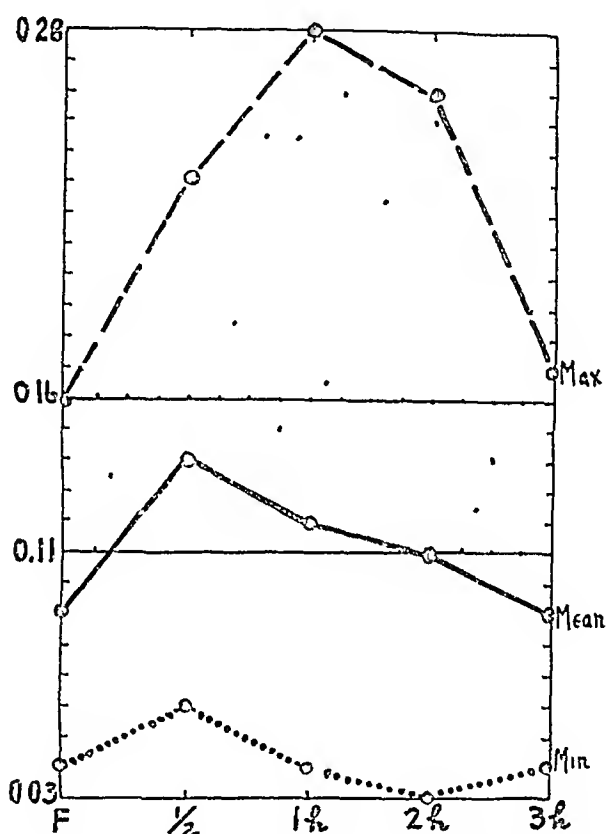


Chart 1—Three hundred normal persons. Maximum, mean and minimum after 100 gm glucose. Normal zone = band between horizontals at 0.11 and 0.16 per cent. Suspicious zone = dotted area.

2 The large range of high values is conspicuous from the shaded area. One may be skeptical of such figures as 0.26 and 0.28 per cent. Definition of the import of values of 0.17 per cent and over can justly be made only in the future when the after-history of these or similar exceptional subjects shall have been reported.

3 The frequency of these values above the average is startling, for they occur among the 300 one hour values in 13 per cent, and among the 158 half hour values in 20 per cent.

4 Of the three hour values 41 per cent read 0.10 per cent or more, in other words, more than the average preformed figures of the series. While this is at variance with the statement not infrequently

made that the three hour figure in normals is regularly equal to the initial figure, or even less, the latter statement is true of a large number of the curves when considered individually. This secondary hypoglycemia is interesting though explanations of it seem to be still rather in the domain of theory, possibly hyperassimilation.

*Comparison of 100 Gm Glucose with Other Doses of Glucose*—Table 5 shows both average and maximum values, with the peak in each composite curve printed distinctively for emphasis. The different doses are arranged in order of magnitude of the acme, and when two doses were each followed by the same acme, then that dose is put first whose curve showed the highest second value. The averages are also shown in Chart 2 and the maximums in Chart 3. Criticism can be made more concisely after showing the related tables.

TABLE 5—COMPARISON OF CURVES OF NORMAL PERSONS AFTER VARYING DOSES OF GLUCOSE

(The peak of each curve is emphasized by different type)

Dose, Gm	Blood Sugar			
	½ Hour	1 Hour	2 Hours	3 Hours
<b>Averages</b>				
150-200	0 16	0 15	0 12	0 10
50	0 14	0 14	0 10	0 10
Consolidated 20-200	0 14	0 12	0 11	0 09
70-100	0 14	0 12	0 11	0 09
20-25	0 10	0 12	0 11	0 09
<b>Maximums</b>				
70-100	0 23	0 28	0 26	0 17
150-200	0 23	0 26	0 16	0 13
50	0 20	0 19	0 17	0 14
20-25	0 14	0 16	0 10	

The highest peak with the smallest dose of glucose is as great as the average peak for the largest dose of glucose (Table 5 and Charts 2 and 3). So it seems fairly reasonable to say that curves vary at least as much owing to individuals as owing to the size of the dose. The reaction of the same subject to various doses of glucose was studied by Jacobsen,<sup>9</sup> Boe,<sup>10</sup> Bergmark,<sup>11</sup> Sakaguchi,<sup>12</sup> Bailey,<sup>13</sup> Strouse,<sup>14</sup> MacLean and De Wesselow,<sup>15</sup> and Spencer.<sup>16</sup> As little as 5 gm glucose was shown by MacLean to produce an appreciable rise and that after a dose of about 25 gm was reached further increases did not increase the rise but merely prolonged it.

10 Boe, G. *Biochem Ztschr* **58** 106 (Oct 29) 1913

11 Bergmark. *Jahrb f Kinderh* **80** 373, 1914

12 Sakaguchi, K. *Mitt d med Fakultat der kaiserlich Univ zu Tokyo* **20** 345 (Oct 11) 1918

13 Bailey, C. V. *Am J M Sc* **157** 221 (Feb) 1919

14 Strouse, S. *Some Variations in Normal Blood Sugar*, *Arch Int Med* **26** 751 (Dec) 1920

15 MacLean, H., and De Wesselow, O. L. V. *Quart J M* **14** 103 (Jan) 1921

16 Spencer, J. C. *Quart J M* **14** 314 (July) 1921

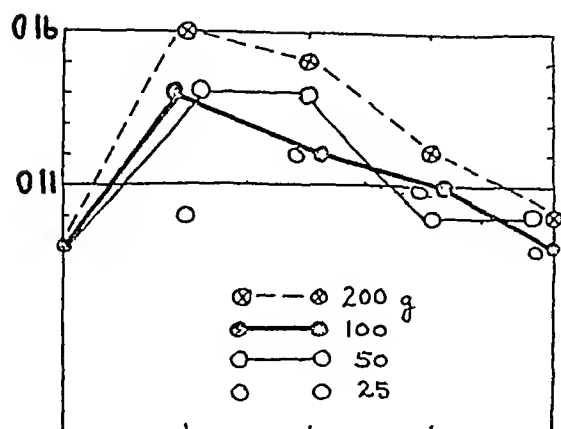


Chart 2—Normal persons Means after different doses of glucose

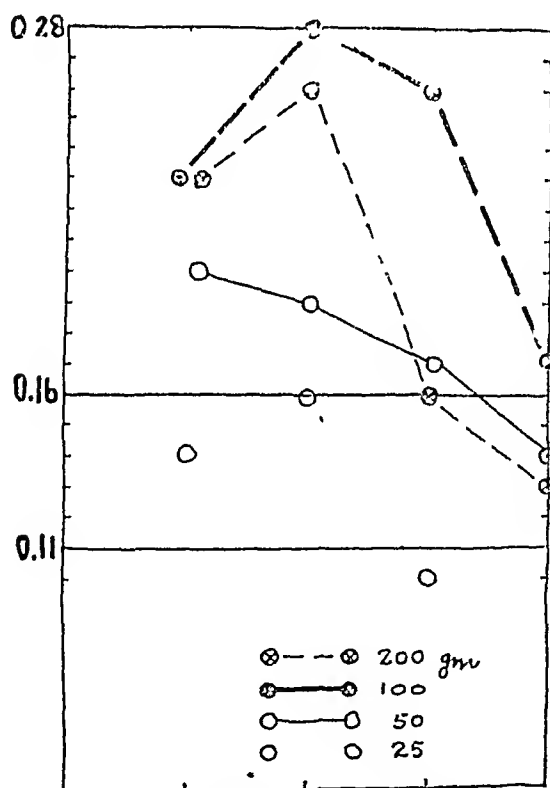


Chart 3—Normal persons Maximums after different doses of glucose

Sakaguchi made the point that the larger doses were characterized largely by the later acme. Staub<sup>17</sup> later published two interesting papers along the same line, but his doses of less than 25 gm glucose caused so small a glycemic reaction that his procedure is not appealing, especially in view of the observation of Benedict, Osterberg and Neuwirth<sup>18</sup> that more than 20 gm glucose were necessary to get results.

The normal range appears from Chart 2 to be surprisingly conveniently schematic. For it is seen that any dose of glucose, from 25 to 200 gm, produces blood sugars falling within a belt delimited by 0.11 and 0.16 per cent. This normal range is easy to remember because general opinions agree, more nearly than on any other standards for blood sugars, on these two points: (1) 0.11 per cent is the highest fasting value which may be called normal, and (2) 0.16 per cent is the threshold above which glycosuria may be expected. In the words of MacLean and De Wesselow, "The hyperglycemia, resulting from the ingestion of carbohydrates, appears in the normal person to be limited to about this level—the threshold level for glycosuria—and cannot easily, if at all, be forced above it." Hence, this range is emphasized by two horizontal lines on each chart in this paper, in order to serve as a visual and actual basis of comparison rather than the base line, which here happens to be 0.03 per cent.

*The Maximum*—While values above 0.16 per cent may fairly be termed "unusual," to call them "abnormal" seems likely to be unnecessarily alarming, since maximal Table 7 shows that any test load (except 50 gm starch, 25 gm glucose or 75 gm fat) may be followed by values of 0.17 or more. The frequency of such unusual values was about one in seven, more exactly, 14 per cent of 452 curves for the seven loads not just excepted. This fact affords helpful confirmation of the importance above insisted on of the dotted doubtful zone in Chart 1. At the same time, to carry out this argument to the limit, we should have to diagnose as normal curves any whose acme was 0.28 per cent or less. This doctrine would generally be considered rash, as overlooking often just the early cases we wish to detect. Hence, we may say, as others have before, that a single high value, however suspicious, requires further evidence. It would be interesting to hear from someone doing frequent glucose tolerance curves how low the reaction may be, and how frequent low reactions are in diabetics who clinically seem severe, and, conversely, how high the reaction may be in clinically mild but definite diabetes. These two paradoxes have been shown by Allen to exist in animals, "The results of single doses of

17 Staub, H. *Biochem Ztschr* **118** 93 (June 27) 1921, *Ztschr f klin Med* **91** 44, 1921.

18 Benedict, S. R., Osterberg, E., and Neuwirth, I. *J Biol Chem* **34** 232 (April) 1918.

sugar are not infallible and special circumstances may cause a mildly diabetic animal to show an apparently better assimilation than one that is not quite diabetic " <sup>19</sup>

The time of the acme (average Table 6) was at the half hour, rather than the hour (with the single exception of the from 20 to 25 gm glucose load). This supports those observers who have insisted on taking the blood at 15 and 30 minutes after eating e g., Jacobsen, Hopkins, <sup>20</sup> Sakaguchi. Indeed, the half hour blood sugar seems at least second in importance only to the fasting figure, or if that be normal—which is usually the fact precipitating a tolerance test—actually the most important determination if only one can conveniently be made. Stated otherwise, for the purposes of any practitioner who meets difficulties in securing blood samples and therefore wishes to take the smallest possible number, the present study leads me to believe that venipuncture at the time of the patient's first visit yields the smallest amount of

TABLE 6—AVERAGE CURVES IN NORMAL PERSONS WITH DIFFERENT LOADS

Load, Gm	Blood Sugar			
	½ Hour	1 Hour	2 Hours	3 Hours
150-200 glucose	0.16	0.15	0.12	0.10
50-100 cane sugar	0.15	0.14	0.12	0.10
70-100 starch	0.15	0.14	0.12	0.11
50 glucose	0.14	0.14	0.10	0.10
100 levulose	0.14	0.13	0.12	0.11
70-100 glucose	0.14	0.12	0.11	0.09
50 starch	0.14	0.12	0.09	
Mixed meal	0.13	0.12	0.11	0.11
20-25 glucose	0.10	0.12	0.11	0.09
10-75 fat	0.10	0.10	0.10	0.10

information possible to derive from the labor expended. Occasionally one has absolutely no choice when the patient is on the wing through the city, but this is relatively rare. One does not hesitate to insist on a second visit one hour after an Ewald test breakfast, although both extraction and chemical analysis of gastric contents are vastly quicker and cheaper than extraction and analysis of blood. Yet the one hour interval is less significant and probably very much less significant than is the time relation in interpreting the blood sugar percentage. Furthermore, the size and even the general nature of the preceding meal is not easily estimated, much less is it a standard test. If the test is worth doing at all, surely it deserves as much precision as is accorded to the routine stomach test breakfast. Two values are far more than twice as helpful as one, and if the two selected be the fasting and half-hour, then they generally tell nearly as much as five values. In office practice, therefore, the patient should come before breakfast or just before lunch or even

<sup>19</sup> Allen, F. M. J. Exper. M. **31** 381, 402 (April) 1920

<sup>20</sup> Hopkins, A. H. Am. J. M. Sc. **149** 256 (Feb.) 1915

supper for a so-called preformed blood sugar, eat a test meal and in half an hour have another blood sample taken. It is important to secure a specimen of urine at the time of each puncture. The nature of the test load matters less than its invariability. I confess to a preference for two shredded wheat biscuits and three ounces of milk, i. e., carbohydrate 50 gm, protein 9 gm, fat 3 gm. This combination is about as purely carbohydrate a meal as is edible, is accurate, cheap, easily kept ready when the office is in the home, and may claim the attention of physicians who dislike the administration of pure glucose to suspected diabetic patients. Tachau<sup>21</sup> advised 50 gm white bread. This test load is practically the Ewald breakfast and therefore has struck me as of service in two directions when a patient has gastric symptoms.

TABLE 7—MAXIMAL VALUES IN NORMAL PERSONS WITH DIFFERENT LOADS

Load Gm	No of Curves	Blood Sugar					
		Values 0.17% or More		½ Hour	1 Hour	2 Hours	3 Hours
		Number	Per Cent				
1 70-100 glucose	300	38	13	0.23	0.28	0.20	0.17
2 150-200 glucose	16	6	37	0.23	0.26	0.16	0.13
3 70-100 starch	19	5	26	0.21	0.19	0.16	0.13
4 50-100 cane sugar	26	8	31	0.20	0.20	0.20	0.15
5 50 glucose	21	4	19	0.20	0.19	0.17	0.14
6 Mixed meal	57	3	5	0.18	0.17	0.14	0.16
7 100 levulose	13	1	8	0.14	0.17	0.12	0.11
	452	65	14				
8 50 starch	4			0.16	0.14	0.12	0.12
9 20-25 glucose	16			0.14	0.16	0.10	
10 10-75 fat	7			0.10	0.10	0.13	0.11

In the maximal Table 7 the time of the acme was less notable, being at the half-hour with only about half the loads and with the other half at the hour period.

*The Size of the Minimum*—Secondary or reactive hypoglycemia after the hyperglycemia is seen in average Table 6, for the three hour value following 100 gm glucose and following from 20 to 25 gm glucose. The former is a large group and the finding, therefore, is significant. These subnormal levels consequent on the rise have been noted by Liefmann and Stern,<sup>22</sup> Bonniger,<sup>23</sup> Lépine,<sup>24</sup> Reicher and Stein,<sup>25</sup> Frank, Bang,<sup>26</sup> Bergmark, Sakaguchi, Kasai and Kinyosai,<sup>27</sup>

21 Tachau, H. *Deutsch Arch f klin Med* **109** 569 (Feb 18) 1913

22 Liefmann, E, and Stern, R. *Biochem Ztschr* **1** 299 (July 18) 1906

23 Bonniger, M. *Deutsch med Wchnschr* **34** 715, 780 (April 30) 1908

24 Lépine, R. *Le diabete sucre*, Paris, 1909, p 198

25 Reicher, K, and Stein, H. *Verhandl d deutsch Kong f inn Med* **27** 401 (April) 1910

26 Bang, I. *Der Blutzucker*, Wiesbaden, 1913

27 Sakaguchi, K, Kasai, T, and Kinyosai. *Mitt d med Fakultat der kaiserl Univ zu Tokyo* **14** 112 (June 4) 1915

Hahn and Offenbacher,<sup>28</sup> Grunthal,<sup>29</sup> Goetzky,<sup>30</sup> MacLean and De Wesselow, Folin and Berglund<sup>31</sup> Just why the phenomenon is not seen elsewhere in the table is not clear Its significance has not been proven, but the usual and the most plausible explanation so far offered is that it is due to hyperassimilation once the functioning of the liver (?) has become well started

The time of the minimum has been variously stated from Jacobsen's 105 minutes up to three hours, usually at two hours Let us consider this topic together with the practical suggestion which is more or less definitely apparent in the writings of Hamman and Hirschman, MacLean and De Wesselow, and of Staub, that one requisite of the future standard load should be that it be small enough to permit the blood sugar to return to the preformed level within the period of practicable observation We might, accordingly, cease to heed among the rival test loads all those which are followed at the end of three hours by a value averaging 0.11 or more Application of this suggestion to average Table 6 would indicate the probable undesirability of the following 50 or more gm cane sugar, 70 or more gm starch, 100 gm levulose, and mixed meals, unless definitely restricted In addition, in case the latest blood to be drawn is two hours p c, one may discard all the other loads except 50 gm glucose or starch One wonders whether this solution is too simple to be satisfactory

*Choice of Test Substance and Dose*—Fat is useless, as it produces no glycemic reaction—witness row 10 in average Table 6 which absolutely confirms the individual cases of Jacobsen and others Protein may effect a rise if the subject has a low carbohydrate tolerance, or may effect no reaction if the tolerance be normal, as indicated by the varying results of Jacobsen, Rolly and Oppermann,<sup>32</sup> Welz,<sup>33</sup> Strouse, Stein and Wisely,<sup>34</sup> Allen,<sup>35</sup> Sakaguchi, Mosenthal, Clausen and Hiller,<sup>36</sup> Jacobsen and Edwards,<sup>37</sup> MacLean and De Wesselow, and Cammidge<sup>38</sup> The difference in results probably is due to the degree of diabetic tendency the more abnormal the person the greater is the glycemic

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28 Hahn, A, and Offenbacher, R *Deutsch med Wchnschr* **45** 1298 (Nov 20) 1919

29 Grunthal, P *Beitr z Frage des renalen Ursprungs der Schwangerschaftsglykosurien*, Inaug-Diss, Breslau, 1920

30 Goetzky, F *Ztschr f Kinderh* **27** 195 (Oct 18) 1920

31 Folin, O, and Berglund, H *J Biol Chem* **51** 213 (March) 1922

32 Rolly, F, and Oppermann, F *Biochem Ztschr* **48** 187, 1913

33 Welz, A *Arch f exper Path* **73** 159, 1913

34 Strouse, S, Stein, I F, and Wisely, A *Bull Johns Hopkins Hosp* **26** 211 (June) 1915

35 Allen, F M *Am J M Sc* **153** 313 (March) 1917

36 Mosenthal, H O, Clausen, S W, and Hiller, A *The Effect of Diet on Blood Sugar in Diabetes Mellitus*, *Arch Int Med* **21** 93 (Jan) 1918

37 Jacobsen, A T B, and Edwards, H *Am J M Sc* **159** 833 (June) 1920

38 Cammidge, P J *Brit M J* **2** 586 (Oct 15) 1921



reaction after protein One notices incidentally that many, if not all, of the students of the effect of protein have included some fat, if only the portion usual in lean meat Practically fat free protein, like egg white, cod or haddock, might exert a greater glycemic effect As to carbohydrates, the differences in effect appear too small to determine any special preference Regarding the dosage, however, we may read more out of maximum Table 7 For there the twenty curves with 50 gm starch or from 20 to 25 gm glucose show a common characteristic the blood sugar in no instance exceeded 0.16 per cent As this figure, perhaps, has received as much proof as any of being the upper usual limit of sugar freedom, one may revise Naunyn<sup>39</sup> slightly by saying that hyperglycemia or glycosuria *e amylo*—provided the dose of starch be from 40 to 60 gm—indicates a carbohydrate weakness more delicately than the massive loads of glucose so generally used, and, simultaneously, one may urge that the 50 gm starch load has advantage of conservatism and, hence, wider applicability For although several authorities on diabetes have stated that they have never seen harm from 100 gm loads of glucose, danger to a subnormal pancreas may be feared by analogy with the studies on experimental diabetes in animals reported by Thirolloix and Jacob,<sup>40</sup> Allen,<sup>41</sup> and Jensen and Carlson<sup>42</sup> For these reasons Joslin and others have always been chary of using glucose tests

Pure glucose must be granted to be preferable scientifically For even if starch be as rapidly digested, Folin and Beiglund have demonstrated that polysaccharids may pass into the blood stream and out again through the kidneys intact and, therefore, very possibly unutilized Really small doses of glucose, down to even 10 gm were suggested by Hamman and Hirschman who wrote "The general features of the diabetic blood sugar curve are faithfully reproduced by patients receiving, on account of the severity of their disease, smaller amounts of glucose Apparently the duration of the reaction is a more important index of the severity than is the height" Salomon<sup>43</sup> disapproved the routine administration of even 50 gm glucose, though he thought it safe in cases with continuous low glycosuria, only after this dose had failed to cause a rise in blood sugar did he think it wise to use 100 gm Staub later noticed in the literature that with smaller doses the duration of the hyperglycemia was shortened, and from this he antici-

39 Naunyn, B. *Deutsch Klin* 3 1 1902, also *Gesammelte Abhandlungen*, Würzburg 2 1039, 1909

40 Thirolloix, J., and Jacob. *Compt rend Acad d sc*, Par 154 377, 1912

41 Allen, F. M. *Glycosuria and Diabetes*, Harvard University Press, Cambridge, 1913

42 Jensen, V. W., and Carlson, A. J. *Am J Physiol* 51 423 (April) 1920

43 Salomon, H. *Munchen med Wchnschr* 68 386 (April 1) 1921

pated, and found, that with the smaller doses the whole course of the reaction might be compressed into a proportionately shorter time period, thus rendering this functional test simpler

## DIABETES

The number of curves collected on diabetics without known hypertension, nephritis, hepatic or endocrine disease totalled 131. The conditions mentioned are examined separately below, and confirm the findings of prior observers that diabetes cannot be diagnosed from curves in the presence of these other conditions, which independently may cause marked alimentary hyperglycemia.

TABLE 8 — FREQUENCY OF DIFFERENT LOADS IN DIABETES (UNCOMPLICATED)

100 gm glucose, when blood sugar (F) was 0.11 per cent or less	40
100 gm glucose, when blood sugar (F) was 0.12 per cent or more	54
50 gm glucose, when blood sugar (F) was 0.11 per cent or less	6
50 gm glucose, when blood sugar (F) was 0.12 per cent or more	4
50 gm starch	2
25 gm starch	2
Mixed meal containing at least 40 gm carbohydrate or 0.5 gm/l, when blood sugar was 0.11 or less	17
Mixed meal containing at least 40 gm carbohydrate or 0.5 gm/l, when blood sugar was 0.12 or more	6
	131

TABLE 9 — ONE HUNDRED GRAMS GLUCOSE IN FORTY DIABETIC PATIENTS WHOSE BLOOD SUGAR FASTING WAS NORMAL, TOGETHER WITH COMPOSITE CURVES REPRODUCED FROM NORMAL TABLE 4

	Blood Sugar				
	Fasting	½ Hour	1 Hour	2 Hours	3 Hours
Mean	0.09	0.18	0.20	0.15	0.10
Minimum	0.05	0.11	0.12	0.08	0.08
Maximum	0.11	0.27	0.40	0.50	0.14
Normal					
Mean	0.09	0.14	0.12	0.11	0.09
Maximum	0.16	0.23	0.28	0.26	0.17

For purposes of study, the curves have been sorted according to the several test loads and also in some cases further separated according to whether the blood sugar fasting was normal, 0.11 per cent or less, or elevated, 0.12 per cent or more. The number in the several groups may be surveyed in Table 8, after which each group will be exhibited by a tabular summary with discussion compressed into a legend.

It is in these diabetics with normal preformed blood sugars (Table 9) that curves are of particular interest. The highest blood sugar found after 100 gm glucose in any diabetic whose fasting blood sugar was 0.11 per cent or less was the extraordinary value of 0.50 per cent (at the end of one and one-half hours as reported by Rohdenburg, Bernhard and Krehbiel,<sup>44</sup> here included in the two hour period).

<sup>44</sup> Rohdenburg, G. L., Bernhard, A., and Krehbiel, O. *Am. J. M. Sc.* 159:577 (April) 1920.

TABLE 10—ONE HUNDRED GRAMS GLUCOSE IN FIFTY-FOUR DIABETIC PATIENTS WHOSE BLOOD SUGAR (F) WAS 0.12 PER CENT OR MORE

	Blood Sugar				
	Fasting	½ Hour	1 Hour	2 Hours	3 Hours
Mean	0.17	0.25	0.27	0.25	0.21
Minimum	0.12	0.16	0.10	0.10	0.08
Maximum	0.31	0.43	0.49	0.45	0.50*

\* From this table it is seen that the highest value 0.50 per cent (at the end of three hours, Hopkins, 1915) is no greater than in Table 9, contrary to expectation, but that average, minimal and maximal curves are here much higher, as anticipated. A further difference is that the average curve for these diabetics shows a slower decline than in the prior table. Here the mean value at three hours is still noticeably above the preformed figures (Hamman's plateau).

TABLE 11—FIFTY GRAMS GLUCOSE IN SIX DIABETIC PERSONS WHOSE BLOOD SUGAR FASTING WAS 0.11 PER CENT OR LESS

	Blood Sugar				
	Fasting	½ Hour	1 Hour	2 Hours	3 Hours
Mean	0.08	0.12	0.12	0.14	0.13
Minimum	0.06	0.09	0.07	0.10	0.13
Maximum	0.11	0.15	0.24	0.20	0.13
Normal					
Mean	0.09	0.14	0.14	0.10	0.10
Maximum	0.10	0.20	0.19	0.17	0.14*

\* In this table the values are most confusing, inasmuch as they are at several periods actually less than the normals, possibly owing to preceding undernutrition. However they do show the same prolongation of the diabetic reaction pointed out in the preceding curve.

TABLE 12—FIFTY GRAMS GLUCOSE IN FOUR DIABETIC PATIENTS WHOSE BLOOD SUGAR FASTING WAS 0.12 PER CENT OR MORE

	Blood Sugar				
	Fasting	½ Hour	1 Hour	2 Hours	3 Hours
Mean	0.14	0.19	0.22	0.20	0.19
Minimum	0.13	0.17	0.20	0.11	0.11
Maximum	0.15	0.23	0.26	0.26	0.26

\* In this table both mean and maximum show the anticipated excess over the normal standard.

TABLE 13—FIFTY GRAMS STARCH IN DIABETES

	Blood Sugar				
	Fasting	½ Hour	1 Hour	2 Hours	3 Hours
Dr. A, a clinically mild diabetic, aged 63	0.11		0.23	0.24	0.22
Normal					
Mean	0.09	0.14	0.12	0.09	
Maximum	0.09	0.16	0.14	0.12	0.12*

\* This table reports a case seen by me which supports strikingly the argument for this test load as urged in the text. This marked glycaemic reaction despite the normal fasting value seems especially interesting and is I believe much commoner than currently conceded. We have seen it also in some other cases but omit them as they are neither so striking nor numerous enough as yet to be statistically presented. The absence of the half hour blood sugar in this case is regrettable. Albumin, hypertension and hard arteries were not present.

TABLE 14—FROM 25 TO 30 GM STARCH IN DIABETES

	Blood Sugar			
	½ Hour	1 Hour	2 Hours	3 Hours
Jacobsen's patient	0.14	0.14	0.10	0.11
MacLenn and DeWesselow's patient	0.11	0.15	0.14	0.12
Normal control	None found*			

\* Such small doses of starch have rarely been reported, but may be inferred from the evidence in this table to be inadequate.

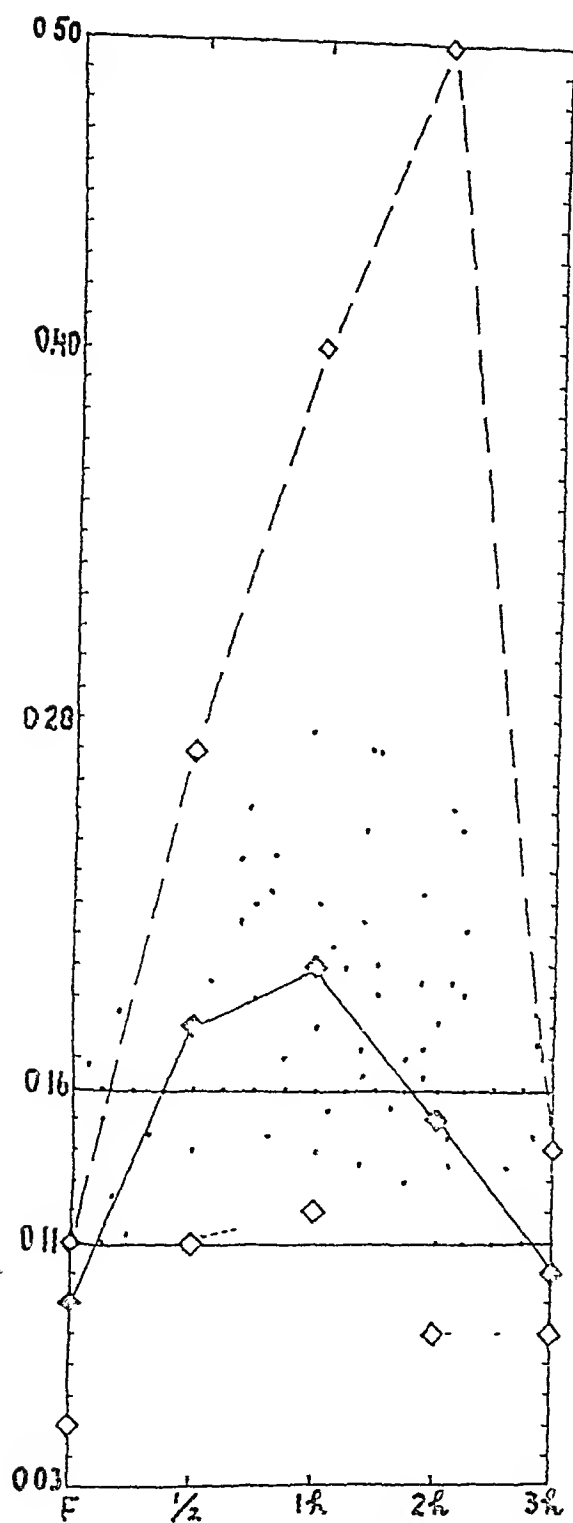


Chart 4—Diabetic patients with normal fasting blood sugar. Maximum mean and minimum after 100 gm glucose. Dotted area is the suspicious zone from Chart 1.

and the next highest 0.40 per cent (at the end of one hour, according to Joslin [unpublished]) The curve had returned practically to normal at the end of three hours Hence, it is conspicuous that a normal fasting sugar by no means excludes the presence of diabetes, and that the entire curve in a diabetic may be normal

Chart 4 proves picturesquely the folly of reassuring any patient on the ground of a normal fasting blood sugar

TABLE 15—MIXED MEALS CONTAINING AT LEAST 40 GM CARBOHYDRATE, OR ABOUT 0.5 GM PER KILOGRAM OF BODY WEIGHT, IN SEVENTEEN DIABETIC PATIENTS WHOSE BLOOD SUGAR (F) WAS 0.11 PER CENT OR LESS

	Blood Sugar			
	½ Hour	1 Hour	2 Hours	3 Hours
Mean	0.09	0.12	0.11	0.10
Minimum	0.03	0.03	0.03	0.07
Maximum	0.11	0.14	0.17	0.13
Normal				
Mean	0.13	0.12	0.11	0.11
Maximum	0.18	0.17	0.14	0.16*

\* This table, like Table 11, is surprising because of the low figures

TABLE 16—MIXED MEALS CONTAINING AT LEAST 40 GM CARBOHYDRATE OR 0.5 GM PER KILOGRAM OF BODY WEIGHT, IN SIX DIABETIC PATIENTS WHOSE BLOOD SUGAR (F) WAS 0.12 PER CENT OR MORE

	Blood Sugar				
	Fasting	½ Hour	1 Hour	2 Hours	3 Hours
Mean	0.14	0.25	0.18	0.11	0.21
Minimum	0.12	0.17	0.14	0.14	0.20
Maximum	0.18	0.34	0.30	0.25	0.21*

\* This table is about what might have been forecast

TABLE 17—FROM 33 TO 100 GM GLUCOSE IN SEVEN DIABETIC PATIENTS WITH ESSENTIAL (?) HYPERTENSION

	Blood Sugar				
	Fasting	½ Hour	1 Hour	2 Hours	3 Hours
Mean	0.18	0.24	0.29	0.29	0.26
Minimum	0.10	0.19	0.24	0.22	0.19
Maximum	0.23	0.29	0.33	0.41	0.39*

\* The 33 gm curves were thought legitimate for inclusion in this table, since they showed actually higher values than the curves following 100 gm In this table the values average higher than those in diabetes simplex in Table 9, and even than those in Table 10

## SUMMARY

Standards of blood sugar response to carbohydrate intake are presented on the basis of more than 900 curves and 4,000 individual determinations

The fasting value in 431 apparently healthy persons averaged 0.09 per cent The unusual figures, however, of 0.12 to 0.16, were reached in as many as seven per cent of these normals, thus leading to the

alternatives clinical judgment of normal metabolism is untrustworthy, or a considerable number of normals exhibit suspiciously large fasting figures

The statement that normal persons do not have sugar in the urine after eating 100 gm glucose is disputed on the ground of evidence here collected that in 129 curves glycosuria was noted in 40 per cent. This astounding discovery would be even more extraordinary—and reassuring in prognosis—if the urine had been examined at the time of each blood letting instead of only once as was so often the case, if examined in all the 300 curves instead of only 129, and if the after histories of these subjects were known ten years later

The normal postprandial curve averaged 0.14 (one-half hour), 0.12 (one hour), 0.11 (two hours), and 0.09 per cent (three hours). The average acme of 0.14 per cent was lower than the value usually postulated as the upper limit of normality, namely, 0.16 per cent.

A normal zone for the glycemic reaction stands out graphically from 0.11 to 0.16 per cent no matter whether the dose of dextrose varied from 20 to 200 gm. Loads of less than the usual 100 gm stimulate adequate reactions, and have the presumptive advantage of avoiding the damage which is both possible theoretically and, in fact, suggested by the annual glucose tests reported by Ohler.<sup>45</sup>

A suspicious zone of high normal reactions appears wider than currently visualized. For values from 0.17 up to 0.28 per cent occurred frequently, namely, in 17 per cent of the analyses after 100 gm glucose.

In diabetes concern is primarily aroused when the fasting blood sugar is 0.11 per cent or less, for when that level is exceeded, a curve is superfluous and possibly an insult to an injured function.

Let us not forget the warnings indicated by the work of Kawachi,<sup>46</sup> of Martius,<sup>47</sup> of Allen,<sup>19</sup> and of Ohler.<sup>45</sup> Kawachi said that the surprisingly great frequency of more or less enduring functional damage by a single overstrain of the sugar utilizing power has been overlooked by failure to continue regular tests for a time after the first disappearance of the glycosuria. Out of the forty persons without metabolic disease reproduced by Martius, the glycosuria after from 25 to 200 gm glucose lasted in 40 per cent ten days, or longer, even twenty-nine, thirty and thirty-two days.

Allen's statement is "In the early stage, glucose is more powerful than starch in producing diabetes, and animals which are progressing

45 Ohler, W. R. *M. Clinics N. America* 5:1465 (March) 1922.

46 Kawachi, S. *Beitrag zur Kenntnis von der alimentaren Glykosurie e saccharo*, Inaug.-Diss., Rostock, 1902.

47 Martius, F. *Konstitution und Vererbung*, Berlin, 1914, p. 117.

toward complete recovery on starch diet can be sent into hopeless diabetes by admixture of glucose" <sup>19</sup>

Ohler has reported several cases in which glucose tolerance tests were done three times at intervals of about one year. In Case 4 (M C) the progressive fall of tolerance may, indeed, be due to her free diet, but, on the other hand, it may also be ascribable to damage by the glucose load.

In cases with normal fasting blood sugars appalling postprandial peaks are seen, even 50 cg per 100 c c, thus manifesting the imprudence of denying diabetes because the fasting figure is eleven or less. For treatment such a finding is encouraging, since we want to know the best blood sugar attainable. For diagnosis, on the other hand, we wish the worst blood sugar of the twenty-four hours, and accordingly should secure the blood half an hour after the test load.

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# BLOOD SUGAR STANDARDS

PART II IN CONDITIONS NEITHER NORMAL NOR DIABETIC

HORACE GRAY, M D

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Normal and diabetic blood sugar curves have been shown in Part I at some length, so that in this paper miscellaneous conditions of altered carbohydrate metabolism are condensed into the least possible space. As the aim is conciseness and convenience of reference rather abrupt transitions are unavoidable. The test meal was 100 gm glucose, except in a few cases, whose inclusion was thought legitimate because the curves were, in general, as high as after the usual dose.

TABLE 1—A TWENTY-NINE INSTANCES OF HYPERTENSION WITHOUT NEPHRITIS \*

	Fasting	½ Hour	1 Hour	2 Hours	3 Hours
Mean	0 11	0 19	0 18	0 16	0 13
Maximum	0 16	0 32	0 30	0 34	0 23

B ELEVEN CASES OF NEPHRITIS WITHOUT HYPERTENSION \*

	Fasting	½ Hour	1 Hour	2 Hours	3 Hours
Mean	0 14	0 19	0 23	0 20	(0 24)
Maximum	0 26	0 26	0 44	0 41	(0 46)

\* In either pure hypertension or nephritis the mean (average) composite curve is slightly above normal and the maximum is striking. The relation of hypertension to potential nephritis and potential diabetes has been interestingly discussed by O'Hare (Am J M Sc 160 366 [Sept] 1920).

TABLE 2—A SEVENTY CASES OF RENAL GLYCOSURIA WITHOUT NEPHRITIS

	Fasting	½ Hour	1 Hour	2 Hours	3 Hours
Mean	0 09	0 13	0 12	0 11	0 09
Minimum	0 05	0 07	0 06	0 04	0 05
Maximum	0 11	0 23	0 22	0 32	0 20

B THREE CASES OF RENAL GLYCOSURIA WITH CHRONIC NEPHRITIS

	Fasting	½ Hour	1 Hour	2 Hours	3 Hours
Mean	0 17	0 22	0 28	0 30	0 24
Minimum	0 10	0 18	0 24	0 23	0 10
Maximum	0 20	0 26	0 33	0 41	0 39

Table 2 supports those who have asserted the relative frequency of hyperglycemia in renal glycosuria. For example, in the one hour column, which presents the largest number of figures for analysis, i e, sixty-seven, as much as 13 per cent exceeded 0 16 and 40 per cent exceeded 0 11. On the other hand, the diagnoses are not adequately



proven in all the original articles, hence the data are reproduced to indicate possibilities rather than accepted fact

The second part of Table 2 shows much higher values, which may be due to the nephritis or to larval diabetes

Perhaps the most interesting curves in supposed renal diabetic patients must be omitted here for the sake of brevity. They are (a) two cases (Bailey's M B and Strouse's C F<sup>1</sup>) diagnosed as renal

TABLE 3—SHOWING FINDINGS OF FIFTY-ONE PREGNANT WOMEN WHOSE BLOOD SUGAR BEFORE BREAKFAST WAS 0.11 PER CENT, OR LESS, I. E., FREE FROM SUSPICION OF DIABETES \*

	Fasting	½ Hour	1 Hour	2 Hours	3 Hours
Mean	0.09	0.14	0.14	0.12	0.13
Minimum	0.05	0.10	0.06	0.04	0.09
Maximum	0.11	0.18	0.25	0.21	0.24
Normal					
Mean	0.09	0.14	0.12	0.11	0.09
Maximum	0.16	0.23	0.28	0.26	0.17

\* This table indicates that in pregnancy the average rise is about the same as in normals, but is longer in duration, while the maximal value at most of the periods hardly equals the highest reported in normals

TABLE 4—SHOWING RESULTS OF ADMINISTERING 100 GM. GLUCOSE IN BERGSMAN'S PATIENTS BEFORE AND AFTER DELIVERY (AVERAGES ONLY) \*

	Blood Sugar			
	Antepartum		Postpartum	
	Fasting	1 Hour	Fasting	1 Hour
Group (a)	0.09	0.15	0.09	0.13
Group (b)	0.09	0.16	0.12	0.21
Group (c)	0.13	0.18	0.09	0.17
General average	0.10	0.15	0.10	0.14

\* To study the meaning of curves in pregnancy when the fasting sugar is 0.12 per cent or more one needs pairs of curves, i. e. both before and after delivery. This need has been supplied by Bergsman for twenty-three women. If each pair be grouped according to the B. S. fasting, we find (a) B. S. (I) normal (0.11 or less) in both, 16 curves, (b) B. S. (F) normal only before delivery, 4 curves, (c) B. S. (F) normal only after delivery, 3 curves. The average curve for each of the three groups and their general average both antepartum and postpartum is seen in Table 4. Group (b) may be suspected of a diabetic tendency developing postpartum. Group (c) may be considered a more marked degree of the usual slightly lowered tolerance of pregnancy as seen in Group (a). Knowledge of the body weight in these types would be of real assistance.

glycosuria at first but later (two and fourteen months, respectively) shown by repetition of the curves to be progressing to true diabetes, (b) conversely, cases (Strouse's 1 B and several of Geyelin's<sup>2</sup>) diagnosed when first seen as true diabetes and later under treatment apparently subsiding into the renal type

1 Authorities cited in Part 1 are not repeated here

2 Geyelin, H. R. M. Clinics N. America 4:1375 (March) 1921

TABLE 5—BLOOD SUGAR IN HYPERTHYROID DISEASE

No		Blood Sugar				
		Fasting	½ Hour	1 Hour	2 Hours	3 Hours
9	When B S (fasting) is 0.12 or more					
	Mean	0.13	0.17	0.18	0.18	0.11
	Maximum	0.13	0.17	0.23	0.26	0.13
58	When B S (fasting) is 0.11 or less					
	Mean	0.09	0.16	0.16	0.14	0.11
	Maximum	0.11	0.22	0.26	0.22	0.18
4	After operation					
	Mean	0.08	0.12	0.10	0.09	0.09
	Maximum	0.10	0.12	0.11	0.12	0.09

TABLE 6—SHOWING FINDINGS IN EIGHT CASES OF HYPOTHYROIDISM, CRETINISM OR MYXEDEMA \*

	Fasting	½ Hour	1 Hour	2 Hours	3 Hours
Mean	0.10	0.16	0.15	0.12	0.11
Maximum	0.13	0.19	0.22	0.19	0.16

\* This table shows an average only slightly lower than in the previous table, and what is more surprising distinctly higher than in normal persons. This is at variance with what would be predicted theoretically and, furthermore, with the evidence given by Sakaguchi.<sup>5</sup>

TABLE 7—SHOWING FINDINGS IN HEPATIC DISEASE \*

No. of Cases		Fasting	½ Hour	1 Hour	2 Hours	3 Hours
7	Obstructive jaundice (stone 5, cancer 3)					
	Mean	0.13		0.22	0.23	
	Maximum	0.15		0.32	0.38	
6	Cardiac cirrhosis					
	Mean	0.14		0.18	0.21	
	Maximum	0.18		0.27	0.26	
28	Alcoholic or syphilitic cirrhosis					
	Mean	0.10	0.15	0.17	0.17	0.18
	Maximum	0.15	0.17	0.25	0.31	0.28
10	Catarrhal jaundice					
	Mean	0.10		0.15		
	Maximum	0.12		0.25		

\* In this table the first three groups are more or less abnormal. The relation of cholelithiasis to diabetes has received a rather small amount of attention in the literature and Joslin<sup>6</sup> has suggested that it may not be long before some student will perform sugar tolerance tests upon all the gallstone cases in the hospital in order to disclose latent diabetes. Circulatory hepatic congestion exhibits a distinct and rather late rise, and cirrhosis a moderate rise. Finally, in catarrhal jaundice the glycaemic reaction is normal on the average, but may be excessive.

5 Sakaguchi, K., Kasai, T., and Kinyosai. Mitt. d. med. Fakultät der kaiserlich Universität zu Tokyo, 14:112 (June 4) 1915.

6 Joslin, E. P. M. Clinics N. America 3:877 (Jan) 1920.

From Table 5 it is manifest that (a) hyperthyroidism must be excluded before interpreting high sugar curves as indices of diabetes, (b) that the average lines exceed normal averages (as given in Part I) by a smaller margin than was anticipated from reviewing the conclusions of other writers who have studied individuals, while the maxima for hyperthyroids even fell short of the maxima for normal (Part I),

TABLE 8—FINDINGS IN ELEVEN CASES OF ACROMEGALY OR IN HYPERPITUITARISM AFTER ADMINISTERING 100 GM GLUCOSE \*

	Blood Sugar				
	Fasting	½ Hour	1 Hour	2 Hours	3 Hours
Mean	0.09	0.13	0.17	0.15	0.11
Minimum	0.06	0.06	0.13	0.10	0.09
Maximum	0.13	0.20	0.26	0.20	0.14

\* In this table acromegaly seems to be accompanied by a much less noticeable upset of carbohydrate metabolism than is usually suggested in the literature

TABLE 9—GLUCOSE IN HYPOPITUITARISM OR IN DYPITUITARISM \*

	240 g	Fasting	½ Hour	1 Hour	2 Hours	3 Hours
Bailey's case		0.12	0.32	0.37	0.34	0.27
	70-100 g in 4 Cases	Fasting	½ Hour	1 Hour	2 Hours	3 Hours
Mean		0.11	0.17	0.17	0.14	0.12
Minimum		0.09	0.13	0.12	0.13	0.10
Maximum		0.13	0.20	0.22	0.20	0.14

\* Like Table 6, this table is more nearly normal than was anticipated

(c) that thyroid patients clinically improved by operation show glyceimic reactions not only normal but rather low normals<sup>3</sup> Evidence as to changes in body weight after operation might be instructive

### CONCLUSIONS

The literature has been combed for blood sugar curves in nondiabetic pathology, and the consolidated results are offered as being the broadest based standards up to date

3 Janney, N. W., and Isaacson, V. I. Proc Soc Exper Biol & Med 14:99 (Nov. 21) 1917

# INTRACUTANEOUS REACTIONS IN LOBAR PNEUMONIA TO PNEUMOTOXIN\*

(A REPLY TO DR GEORGE H BIGELOW)

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In a recent communication Bigelow<sup>1</sup> reviews our work on a "Skin Reaction to Pneumotoxin,"<sup>2</sup> and criticizes the theory we suggested as to the probable function of pneumotoxin in the pathology of lobar pneumonia<sup>3</sup> in the following words "The authors' theory of early sensitization against their pneumotoxin is certainly open to question when we consider the absence of any sensitization necessary in the case of the positive Schick reaction, and also the lack of specificity in the toxic radicle as shown by Vaughan's work"

It is not the object of this communication to enter into polemics relating to theoretic interpretations of our findings. Such attempts may be more productive after our present plan of elaborating and extending the work has been carried out successfully. We merely wish to call attention to certain fundamental errors of technic which Bigelow committed, which, in our mind, may explain his failure to corroborate our observations.

Bigelow studied intracutaneous reactions in pneumonia patients, using a preparation of "pneumotoxin" in addition to a number of other pneumococcus antigens and vaccines. He states that "no reactions comparable to those reported by Weiss and Kolmer with their 'pneumotoxin' were obtained with a similar preparation, nor was there any specific absence of reactions as might be expected from an analogy to the Schick test"

It is important to read carefully the technic used by Bigelow in preparing his "pneumotoxin." To quote his own words

The cultures used were from eighteen to twenty-four hour old growths in 100 c c of a 1 per cent glucose beef infusion broth, neutral to phenolphthalein, which was found to correspond to a hydrogen-ion concentration of from 8.0 to 8.2. The growth was centrifuged, and the sediment was washed twice with sterile salt solution, centrifuging after each washing. The ampules were kept on ice until used. No antigen was used more than a week after being put on ice. Antigen 8—After the second washing with

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\*From the Dermatological Research Institute

1 Bigelow, A H. Intracutaneous Reactions in Lobar Pneumonia, Arch Int Med **29** 221 (Feb.) 1922

2 Weiss, C, and Kolmer, J A. A Skin Reaction to Pneumotoxin, J Immunol **3** 395, 1918

3 Weiss, C. The Properties of Pneumotoxin and Its Probable Function in the Pathology of Lobar Pneumonia, J M Research **39** 103, 1918

saline solution, the sediment was taken up in 10 c.c. of a 10 per cent bile solution (Bacto-oxgall was used) and incubated for one hour. Attempts were made to obtain suitable animal membrane for separation of the bile salts from the dissolved pneumococcus substances by dialysis, but it was found more feasible to obtain the separation by precipitation of the proteins with four volumes of absolute alcohol. This was thoroughly shaken, centrifuged, and the sediment again mixed with absolute alcohol. After recentrifuging, the sediment was dried overnight in partial vacuum over sulphuric acid. The residue was weighed, ground with sufficient sodium chlorid to make the final solution physiologic, and taken up by adding distilled water drop by drop while grinding until 0.1 c.c. contained  $\frac{1}{50}$  mg. dried sediment. (Later injections up to  $\frac{1}{40}$  mg. were used.) This was heated to 56 C. for one hour. For this antigen, all the strains of each type were pooled.

Antigen 10—The most important difference between this and the foregoing antigens is that it was at no time raised above 37.5 C. After the second washing with salt solution, the sediment was divided into known amounts and kept on ice. The day of the tests, sufficient of sterile solution of 2 per cent bile plus 0.25 per cent tricresol was added to make 0.1 c.c. contain the equivalent of one twentieth of the growth of pneumococci on 60 c.c. of broth. An incubated solution of 2 per cent bile plus tricresol was used as control.

Antigen 10 differed from all the others in that it was never raised above 37.5 C., while the others were all held at 56 C. for one hour. In the bile solution, whatever endotoxins the pneumococci contains should be liberated.

It was clearly emphasized by Cole<sup>4</sup> and by Weiss and Kolmer<sup>3</sup> that the production of pneumococcus endotoxin in vitro is a matter of the greatest difficulty and requires the strictest attention to details. The following essentials for success have been entirely overlooked by Bigelow:

- 1 Glucose is not desirable in mediums used for preparation of pneumotoxin, for it inhibits its production.

- 2 Pneumotoxin is extremely labile, and loses its potency on standing in the ice chest for two or three days.

- 3 Pneumotoxin is a true protein and is, therefore, precipitated from solution by the addition of alcohol. Bigelow added absolute alcohol to precipitate the bile salts, and thus incidentally precipitated the pneumotoxin.

- 4 Pneumococci that have been subjected to autolysis in the ice chest will not yield the endotoxin on the addition of bile. Bigelow stored his emulsion in the ice chest and "the day of the tests, added solution of 2 per cent bile plus 0.25 per cent tricresol."

- 5 The choice of a bile salt and even of the brand of sodium choleate used is important. Bigelow used "Bacto-oxgall," which does not yield satisfactory results.

- 6 As Cole pointed out, the  $p_H$  of the pneumococcus emulsion must be regarded by means of a buffer system to facilitate the liberation of pneumotoxin. Bigelow overlooked this.

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<sup>4</sup> Cole, R. Toxic Substances Produced by the Pneumococcus, J. Exper. M. 16 644, 1912.

7 Bigelow did not test the toxicity of his preparation by intravenous injections into guinea-pigs, nor its hemolytic action upon erythrocytes, and hence we are not in a position to know whether or not he was dealing with endocellular toxins of the pneumococcus

It is extremely doubtful whether Bigelow was working with the endocellular hemotoxin of the pneumococcus. We rather think he was using an autolyzed vaccine. This is, furthermore, demonstrated by his findings. To quote him again

Special reference must be made to the reactions obtained with Antigen 10 in which the thermolabile toxic substances from the pneumococcus were not destroyed. When used in the strength recommended by Weiss and Kolmer, and in weaker dilutions, severe local reactions were elicited, showing papules becoming pustular with wide zones of erythema and induration up to 12-14 cm in their longest dimension. This was at its height in about thirty hours, when the erythema faded leaving no pigmentation or scaling in any case. The pustule persisted for weeks. This reaction was well marked in both controls and pneumonia cases, the most severe being in a normal control. The control injection of bile and tricresol showed only a small local papule, but none of the violent erythematous and edematous reaction.

It is necessary to refer to our original report<sup>2</sup> to appreciate the differences in the technic and hence in the results obtained in Dr Bigelow's work and in our own.

The technic of preparation and the properties of pneumotoxin have been fully described by us in previous communications<sup>1, 2</sup>. Briefly stated, the hemolytic endotoxin of the pneumococcus was produced as follows: from 1,000 to 1,500 cc of an eighteen hour broth culture of virulent type I pneumococci (Rockefeller Institute) were centrifugalized for one hour in a powerful electric centrifuge at very high speed. The bacterial sediment was washed once in isotonic salt solution, taken up in 5 cc of saline and dissolved in 1 cc of a 2 per cent solution of sodium choleate. The total volume was made up to 30 or 40 cc, the solution was again centrifugalized, to remove any undissolved pneumococci, and tricresol was added up to 0.25 per cent concentration. The "control fluid," containing no toxin, was made similarly. The preparations were preserved in the refrigerator and they were never used when older than eighteen to twenty-four hours, since the toxin deteriorates very rapidly. All preparations were perfectly homogeneous and slightly opalescent.

The method of standardization has been described elsewhere<sup>2</sup>. In these studies we found it impracticable to determine both the minimum lethal dose and minimum hemolytic dose of each lot of pneumotoxin, and we had to satisfy ourselves with testing only three of the five employed. The minimum lethal dose (tested after the total volume had been made up to 100 cc) was about 6 or 7 cc for a guinea-pig weighing from 250 to 300 gm, and the minimum hemolytic dose was from 0.2 to 0.4 cc when titrated in terms of a 1 per cent suspension of washed guinea-pig erythrocytes. The dose of toxin used in skin tests (0.1 cc) represents therefore about one twentieth the minimum lethal dose.

In our preliminary experiments we studied the reaction to pneumotoxin under controlled conditions in guinea-pigs as follows: a series of animals weighing from 250 to 300 gm were given intravenous injections of sublethal doses of the toxin. From four to six weeks later, the intracutaneous skin tests were made on the shaved abdomen, the dose of toxin being 0.1 cc.

We made preliminary anaphylactic experiments to demonstrate the difference in behavior between autolyzed pneumococcus vaccine and

freshly prepared pneumotoxin We observed, "Guinea-pigs sensitized by intravenous injection of sublethal doses of pneumotoxin regularly show hypersensitiveness to the toxin, but only occasionally to the protein of the cell substance of the pneumococcus"

"Normal guinea-pigs, or those sensitized with unrelated proteins, such as egg albumin, serum, leukocytes, blood fibrin or lung exudate of normal dogs, or with normal human serum or with the reagents (sodium choleate, etc) used in preparing the pneumotoxin, do not react to the intracutaneous injection of pneumotoxin

"The animals reacting to the pneumotoxin showed a definite zone of edema and erythema around the point of injection This tissue was excised and histologic sections were made The findings are as follows There is no change in the epidermis, immediately below it and including all of the submucosa to the first bands of muscle, there is an extensive edema and acute congestion and extravasation of erythrocytes The latter are well preserved and widely distributed in the edematous area Through this area are also to be found numerous lymphocytes and plasma cells with occasional polymorphonuclear leukocytes The muscle shows no involvement The predominating change is the hemorrhagic edema in the submucosa This picture is similar to the skin lesion produced by diphtheria toxin

"Contrasted with this is the pustular and nodular appearance of the area in guinea-pigs reacting to the "pneumococcus protein" skin test Sections of these lesions show in some cases the epidermis intact, as likewise the submucosa subjacent and surrounding the hair follicles, others show marked destruction of the epidermis and adjacent submucosa through suppurative processes In the deeper portions of the submucosa and the involved uppermost bundle of muscle, marked changes are present characterized by acute hyperemia and dense collections of polymorphonuclear leukocytes There is present a slight degree of edema and an occasional area of slight hemorrhagic extravasation The predominating changes are the suppuration of the submucosa and muscle"

There is thus a histologic distinction between cutaneous reactions to pneumococcus protein and to pneumotoxin We conclude that skin reaction to pneumotoxin is a manifestation of a hypersensitiveness to a specific toxic protein which has been introduced parenterally into the tissues of the body We shall refer later to this phase of the work

The desirability of discovering a method of studying the immunity to and the mechanism of recovery from pneumonia led us to apply the pneumotoxin skin test to patients suffering from lobar pneumonia in the various hospitals of Philadelphia during the winter of 1917-1918 All the precautions mentioned in connection with the laboratory studies

were observed. Many control patients, normal adults and children and patients suffering from various chronic and acute infectious diseases of non-pneumococcic origin, were tested. The results of the tests done on children are of particular interest because these patients are less prone to be sensitized to various foreign proteins and above all the disease generally runs a more definite course not being complicated by alcoholism, tuberculosis, etc.

The appearance<sup>5</sup> of the skin reaction to pneumotoxin is in all respects similar to that described for the Schick test with diphtheria toxin. Two or three cases tested just prior to crisis showed a strongly positive reaction marked by vesiculation of the surface layer of the epithelium. Other positive cases showed the usual definitely circumscribed area of edema and erythema persisting for three or four days and then gradually fading, leaving a definitely circumscribed scaling area of brownish pigmentation. After injection of the various control fluids in cases of lobar pneumonia (all were used excepting the vaccine), and of pneumotoxin in control cases, the skin remained normal or presented a slight scratch at the point of injection. Occasionally (in one or two cases of streptococcus infection) the entire arm presented a diffuse erythema without a definite area of edema. Such conditions never persisted longer than forty-eight hours and were considered pseudo-anaphylactic reactions.

Summarizing the results of the pneumotoxin skin test applied to adult cases of lobar pneumonia, we may say that a specific reaction was elicited as early as the fifth and as late as the thirteenth day of the disease (two days before and six days after crisis, respectively). In children it was demonstrable about the same time, but was negative immediately or one or two days after the crisis. Patients recovering by lysis reacted as late as the thirty-second day. In general the test was positive in all active cases, that is, throughout the toxemia. Cases earlier than the fifth day were not available. Control patients suffering with bronchopneumonia or acute or chronic infections not of pneumococcic origin, as well as healthy adults and children, did not react.

Attention is again directed to the definite distinction between the skin reaction to pneumotoxin and the allergic skin reactions to pneumococcus protein. As was pointed out in reviewing the work of Clough, Weil, Steinfeld and Kolmer, the latter reaction is generally negative during the course of the disease and occasionally positive after subsidence. The reverse is generally true in the case of the toxin test.

The mechanism of the pneumotoxin skin reaction is left for future investigation. Tentatively we regard the reaction as indicative of a state

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5 We are not referring to its mechanism.



of allergy to pneumotoxin. As we have suggested elsewhere, sensitization takes place during its liberation (by the action of the normal body enzymes on the pneumococci localized in the lung alveoli) at the time of the prolonged chilling of the body due to exposure. Viewed in this light, failure to elicit the reaction in any convalescing patient signifies the establishment of a temporary immunity or the disappearance of the toxin.

# SOME OBSERVATIONS ON THE VALUE OF THE INDEX AND ANGLE OF BORDET-VAQUEZ IN CARDIAC EXAMINATION

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In 1918, Bordet and Vaquez<sup>1</sup> described two methods for measuring enlargement of the left ventricle in the anteroposterior plane or depth. Measurements on the orthodiagraphic tracing or teleoroentgenogram of the heart have been developed to the point where they are essential to careful cardiac study. But they give information concerning only the measurements of the heart in the transverse plane. It can be appreciated how valuable would be additional information concerning enlargement of the left ventricle in the anteroposterior plane. In view of this fact, and because these methods are gaining attention and prominence in the roentgen-ray laboratories abroad, a critical study of the value of these methods was made in a series of seventy subjects and nine anatomic cross sections.

## TECHNIC

Imagine the patient standing, facing the fluoroscopic screen, as the cross section Figure 1 represents, with the target situated 60 cm. from the screen. The diaphragm is shut down to a narrow slit and the tube centered on the apical region of the heart. Then the extreme point to the left, *B*, in the path of the rays *AN*, is marked on the screen at *N*. A strip of lead 10 cm. long is then placed on the screen so that one end coincides with the point *N*, the tube is then moved to the left until the other end of the strip of lead is in the center of the slit formed by the rays, the tube has then been moved to *A'* through a distance of 10 cm., and the diaphragm opened wide, and a second mark *N'* made corresponding to the new extreme point to the left in the path of the oblique rays *A'N'*. The distance *NN'* between the two crayon marks measured in millimeters is that which Bordet and Vaquez have pleased to call the "index of depth."<sup>2</sup> It will

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\* From the Roentgen-Ray Laboratory of the Massachusetts General Hospital.

1 Vaquez, H., and Bordet, E. *The Heart and the Aorta*, Translated by Honey, J. A., and Macy, J., Ed. 2, New Haven, Yale University Press, 1920, pp. 38-56.

2 Morison devised a simple piece of apparatus for reading the index directly. This can be adapted to any screen. Morison, J. M. W. *A Radioscopic Method for Estimating Hypertrophy of the Left Ventricle*, *Arch. Radiol. & Electrotherap.* **23** 282, 1919.



be noted that this method indicates the depth of a point on the posterior surface of the left ventricle, and, for the determination of that point, the principle involved in locating foreign bodies is utilized

Imagine this cross section turned around so that the patient is standing with his back to the screen. In this position the apex of the heart projects to the left of the spine. The patient is then rotated slowly, with the right shoulder as a pivot, the left shoulder gradually becoming more distant from the screen. During this movement the shadows of the various thoracic organs are necessarily modified. The shadow of the vertebral column which was in the middle of the screen is displaced to the left, while that of the left ventricle is transferred to the right. These two shadows traveling in opposite directions cross,

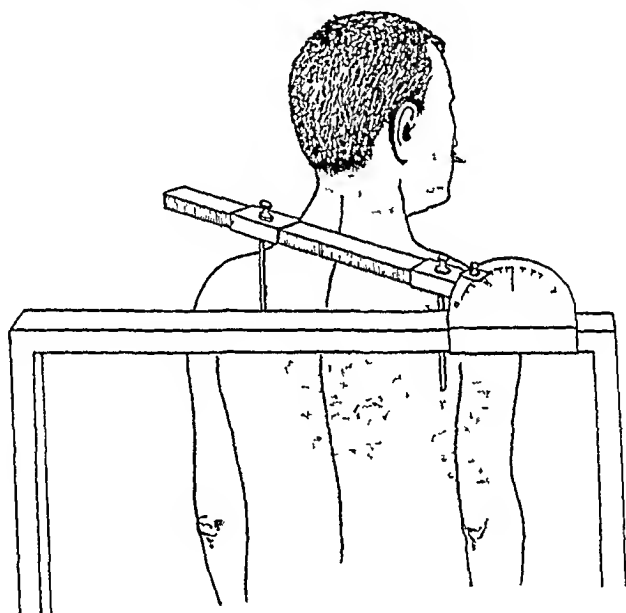


Fig 3—Gonimeter of Vaquez and Bordet (From Bordet and Vaquez)

then the extreme point to the left in the region of the apex approaches the vertebral column and finally disappears behind its shadow. The angle of obliquity formed by the back of the patient with the screen is then measured with the gonimeter devised by Bordet and Vaquez (Fig 3). This they have termed the "angle of disappearance of the apex."

What actually occurs can be seen by reference to Figure 1. If the cross section is rotated as described above until the point *C* coincides with the lateral border of the spinous process, which obtains when the line *DC* is perpendicular to the screen or base line, then the angle of obliquity formed by the section with the screen will be the angle at which the left border of the heart in the region of the apex coincides with or has just disappeared behind the spine.

In addition to the determination of the index and angle measurements, all subjects were examined according to the technic described by Holmes and Ruggles,<sup>3</sup> using the combined fluoroscopic and seven foot teleoroentgenographic observations

#### THEORETIC CONSIDERATIONS OF THE INDEX AND ANGLE

It will be noted that if the left ventricle is increased in the antero-posterior plane or in depth, as shown in Figure 2, when the tube is shifted 10 cm, the oblique rays will meet a point, *B*, at a greater distance from the screen than in Figure 1, and will be projected farther to the left of *N* on the screen and thus increase the distance *NN'* or the index of depth. The distance of point *B* from the screen is thus seen to be the determining factor of the index measurement. It is readily appreciated that in addition to enlargement of the left ventricle in depth the distance *BN* can be increased by anything which tends to increase the distance between the anterior chest wall and the screen

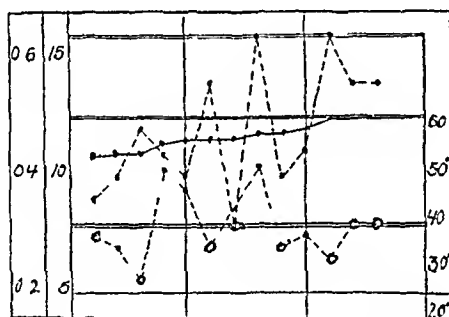


Fig 4—Relationship of index and angle to the cardiothoracic ratio. Ordinates to the left, index in mms, cardiothoracic ratio in decimals. Ordinate to the right, angle. Abscissa, each square represents a case, upper broken line, index, lower broken line, angle. Solid horizontal lines, upper normal levels for each of these measurements.

It will also be observed (Fig 1) that the oblique rays *A'N'* only project points on the posterior surface of the left ventricle which occur in their path, considerable enlargement can exist posteriorly and still be out of the path of these oblique rays, thus exerting no influence on the index of depth.

The enlargement of the right ventricle is largely anterior and therefore will not alter the index measurement.

Theoretically, it would appear that the angle of disappearance of the apex should depend normally to a great degree on the shape of the thorax, being less in the case of a heart in a thorax of round cross section than in the same heart in a thorax whose cross section was

3 Holmes, G W, and Ruggles, H W. Roentgen Interpretation, Philadelphia and New York, Lea & Febiger, 1921, p 124

considerably flattened in the anteroposterior direction. Reference to Figures 1 and 2 shows that in addition the position of point C or the shape of the posterolateral surface of the left ventricle must be taken into account.

# CLINICAL AND ANATOMIC OBSERVATIONS ON THE RELATIONSHIP OF INDEX, ANGLE, AND CARDIO-THORACIC RATIO

Roger Lee<sup>4</sup> called attention to the relationship existing normally between the heart, chest, and age. Saul Danzer<sup>5</sup> expressed this relationship in the form of a ratio in which, normally, the total transverse diameter of the heart is equal to or less than one-half of the widest internal diameter of the chest. In other words, normally the cardio-thoracic ratio equals 0.5 or less.

TABLE 1—MEASUREMENTS FOR NORMAL SUBJECTS

Case	Age	Weight	Height in Inches	Trans- verse, Cm	Longi- tudinal, Cm	Cardio- Thoracic Ratio	Index of Depth, Mm	Angle*	Ant-Post Diameter Chest, Cm †	Shape of Heart ‡
Dr. M. S.	23	166	68	12.9	13.7	0.50	14	40—	23.5	0
Dr. F. R.	23	140	66	11	13	0.44	12	25+	19	V
Dr. E. W.	29	200	72	14.8	15.6	0.48	16	50+	22.3	H
Dr. W. C.	24	185	75	13.9	14.7	0.47	10	45+	22	V
Dr. W. A.	27	145	69	13.1	14.4	0.47	14	35	20.5	0
Dr. E. W.	24	140	67	12.4	15	0.49	15	35—	18.5	0
Dr. M. S.	29	150	72	12.4	14.9	0.47	8	40+	19.5	V
Dr. I. W.	27	172	72	14.5	15	0.50	14	40	20.5	0
Miss A.	23	170	65	12	14	0.50	16	35—	19	H
Miss C.	30	140	66	10.4	13	0.46	11	50+	19	H
Miss D.	23	95	65	9.1	10.5	0.44	10	35	16.2	V
Miss W.	19	125	67	10.2	12.9	0.48	10	35	18.7	V
Miss F.	19	112	63	11.5	13.4	0.49	11	40—	17	0
Dr. E. Y.	26	165	72	11.7	13.3	0.43	9	40—	20.3	V
Miss P.	20	143	65	12.2	13.1	0.48	14		22	H
Dr. W. M.	27	190	72	14.3	16.3	0.46	14		23	0
Mr. M. N.	27	193	66	13.7	14.5	0.48	13		22.1	0
Miss H.	21	135	66	12.6	13.4	0.49	13		19.2	0
Miss H.	19	112	63	10.4	13.1	0.47	13		17	V

\* In angle, + = increase from 2 to 3 degrees, — = reverse

† Taken at level of tenth dorsal vertebra

‡ 0 = oblique, V = vertical, H = horizontal

It will be observed in Figure 4 that normally when the cardio-thoracic ratio does not exceed 0.5, the index does not exceed 16 mm, but the angle does exceed 40 degrees which was taken as the upper normal limit by Bordet and Vaquez. To be sure, the index measurement does exceed their upper normal of 14 mm, but it will be observed from Table 1 that this occurred in well developed, heavy subjects. At the same time, it will be noted that there is no parallelism between the index and angle measurements.

4 Lee, R. I., Dodd, W. J., and Young, E. L. A Study of the Effect of Rowing on the Heart, Boston M. & S. J. **173** 500, 1915.

5 Danzer, Saul C. The Cardiothoracic Ratio. An Index of Cardiac Enlargement, Am. J. M. Sc. **184** 513, 1919.

This same lack of parallelism is noted in Figure 5 in a series of pathologic hearts, and in Figure 6, cross sections of the trunk in the apical region of the heart

The figures derived from these cross sections are offered here merely from a comparative standpoint. It is realized that postmortem changes cause alterations in volume which to a certain extent destroy their value for obtaining exact figures as to size. But they do furnish valuable information concerning the factors involved in cardiac measurements. Concerning the angle measurement, Van Zwaluwenburg says <sup>6</sup> "in our hands this maneuver has been somewhat disappointing, since the exact angle depends to so great a degree on the shape of the thorax."

#### PHYSIOLOGIC INFLUENCES ON THE INDEX OF DEPTH

In view of the transverse cardiothoracic ratio, it was thought that a similar relationship might exist normally between the index and the anteroposterior diameter of the chest. Figure 7 fails to substantiate such a parallelism.

TABLE 2—EFFECT OF RESPIRATION ON THE INDEX OF DEPTH

Quiet Respiration	Forced Inspiration	Forced Expiration
14	24	18
13	11	27
9	20	18
14	10	22
9	11	19
12	17	18

It will be recalled from the paragraph on theoretic considerations that the index would be increased by anything which increased the distance between the anterior chest wall and the screen, this condition obtains in female subjects, and it is readily appreciated that when the breasts are considerably increased in size, proportionate reduction must be made in the index measurement. This is easily obtained by applying the theorem for similar triangles, after the thickness of the breasts has been measured.

It will be observed from a comparison of the index of depth and the form of the heart (Table 1) that the larger values tend to be associated with the horizontal type, while the smaller accompany the vertical type. The reason for this will be discussed in the consideration of pathologic hearts.

Table 2 shows the marked influence that forced respiration exerts on the index measurement. Groedel makes the following statements

<sup>6</sup> Van Zwaluwenburg, J. G. A Plea for the Use of the Fluoroscope in the Examination of the Heart and Great Vessels, *Am J Roentgenol* 7 1, 1920

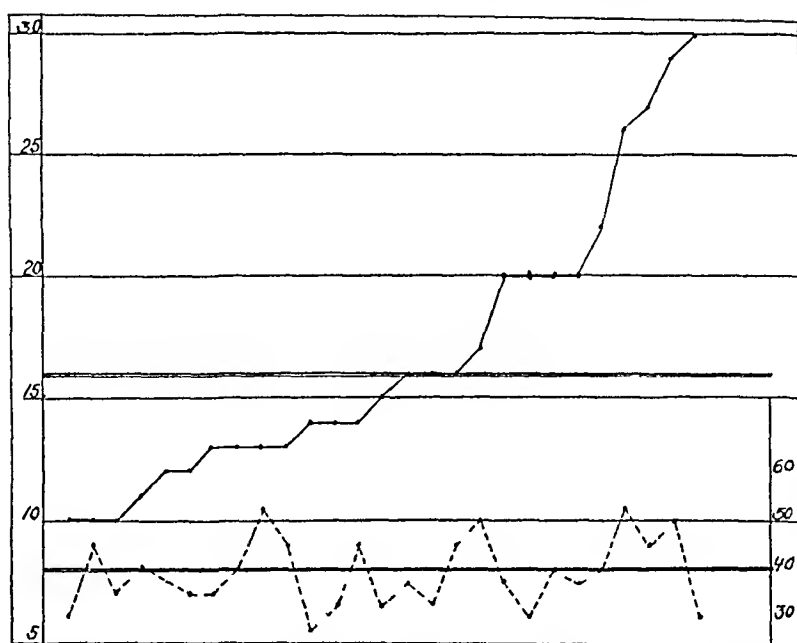


Fig 5—Relationship of angle to index in a series of pathologic subjects Ordinate and abscissa same as in Figure 4 Solid line, index, broken line, angle

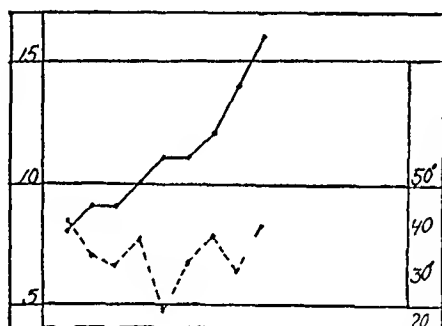


Fig 6—Relationship of angle to index in a series of anatomic cross-sections Ordinate and abscissa same as in Figure 5

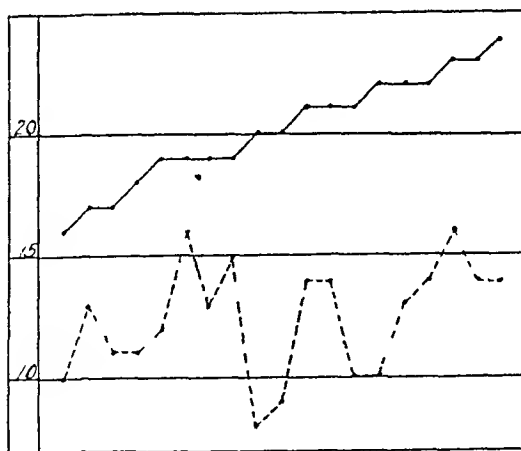


Fig 7—Relationship of index to anteroposterior diameter of the chest Diameter taken at level of tenth dorsal vertebra with calipers Ordinate in centimeters for the solid line, chest diameter, in millimeters, the broken line, index Abscissa, each square a case



concerning the influence of respiration on the heart <sup>7</sup> "Following the force of gravity, the heart moves lower on inspiration, and the apex of the heart turns inward following the directions of the hands of the clock, the opposite occurs on expiration, exact measurements show that on quiet breathing there is no diminution and therefore no change in dimensions" The marked alteration in the normal value of the index during forced respiration suggests the fact that the index measurement cannot be of value where the heart is displaced by pathologic conditions in the lungs, pleura, mediastinum, diaphragm, and perhaps large aneurysms of the aorta

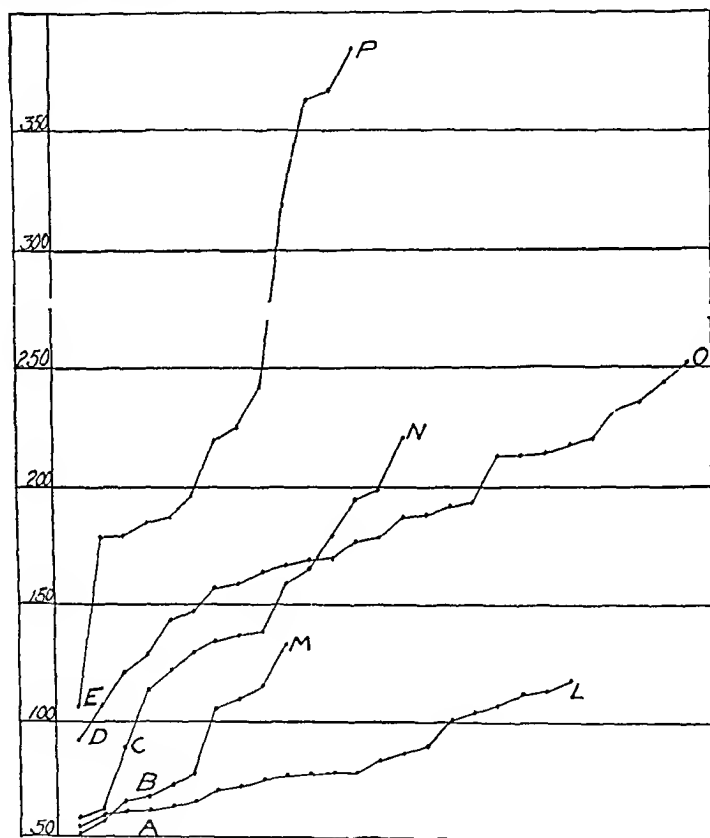


Fig 8—Weights of the left ventricle Charted from Lewis' tables Ordinate, weight in grams, abscissa, each square, a case *AL*, normal cardiovascular controls, *BM*, mitral stenosis predominant valvular lesion, *CN*, mitral stenosis and aortic disease, *DO*, hypertensive heart disease with evidence of chronic nephritis and a systolic blood pressure of 160 mm or more, *EP*, aortic disease predominant

#### OBSERVATIONS ON THE INDEX IN PATHOLOGIC SUBJECTS IN RELATION TO NECROPSY FINDINGS

Since the index has been proposed as a guide to increase in depth of the left ventricle and indirectly to left ventricular hypertrophy, it

<sup>7</sup> Groedel, F M Die Roentgendiagnostik der Herz und Gefaszerkrankungen, Berlin, Herman Meusser, 1912, pp 65 and 69

seems highly desirable to make a general inquiry into the relation of hypertrophy to valvular and hypertensive heart disease to determine if the index measurement is compatible with our knowledge of hypertrophy in these conditions. Lewis<sup>8</sup> has placed the question of hypertrophy and its associations with valvular disease upon a scientific basis by devising a method of dissection of the heart into its separate chambers, which is of much greater exactitude than those customarily

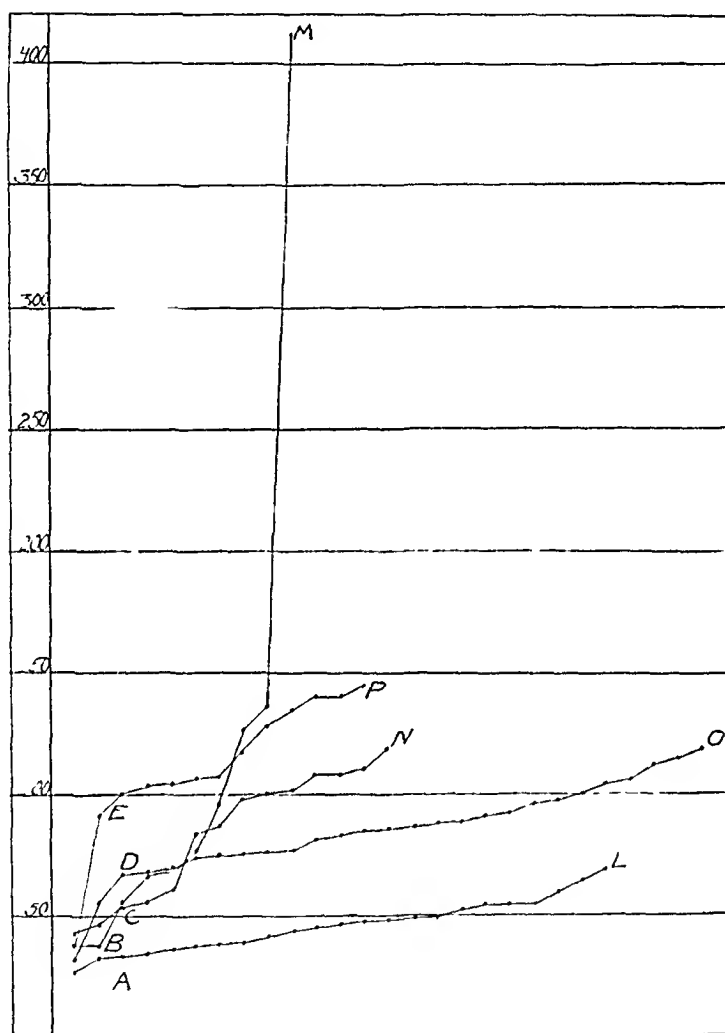


Fig 9—Weights of the right ventricle Legend same as in Figure 8

practiced in the postmortem room. Figures 8, 9 and 10 represent charts which were constructed from his findings in the various affections noted. It will be observed that the order of progression for the separate ventricular weights is normal, predominant mitral stenosis, hypertensive heart disease with and without nephritis, aortic and mitral disease, and finally aortic disease in which we find in general the heaviest

<sup>8</sup> Lewis, T. Observations on Ventricular Hypertrophy, with Especial Reference to Preponderance of One or Other Chamber, *Heart* 5 377, 1913

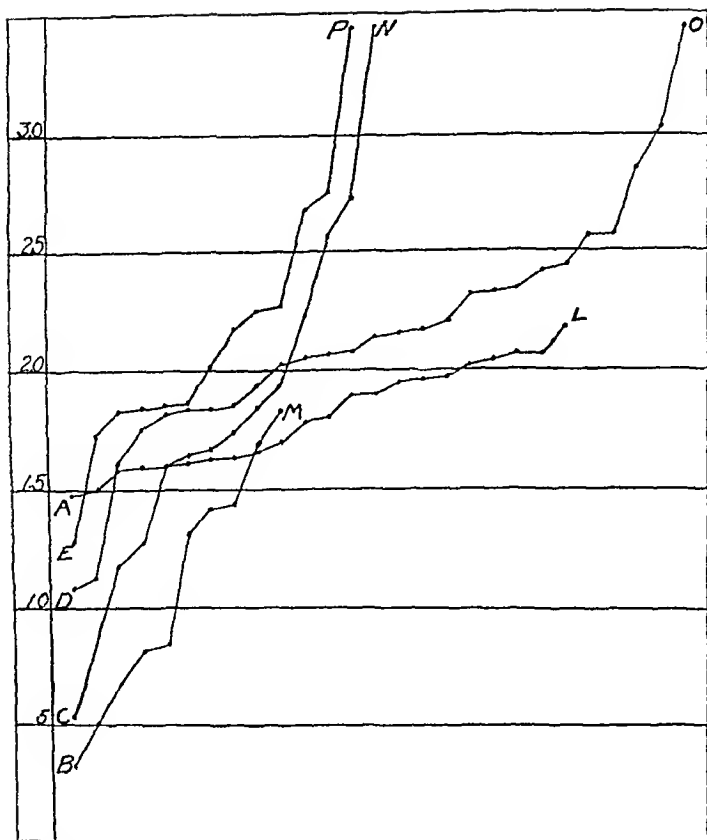


Fig 10—L/R ratio for ventricular weights Ordinate represents the ratio of the weight of the left ventricle to that of the right, otherwise legend the same as in Figure 8

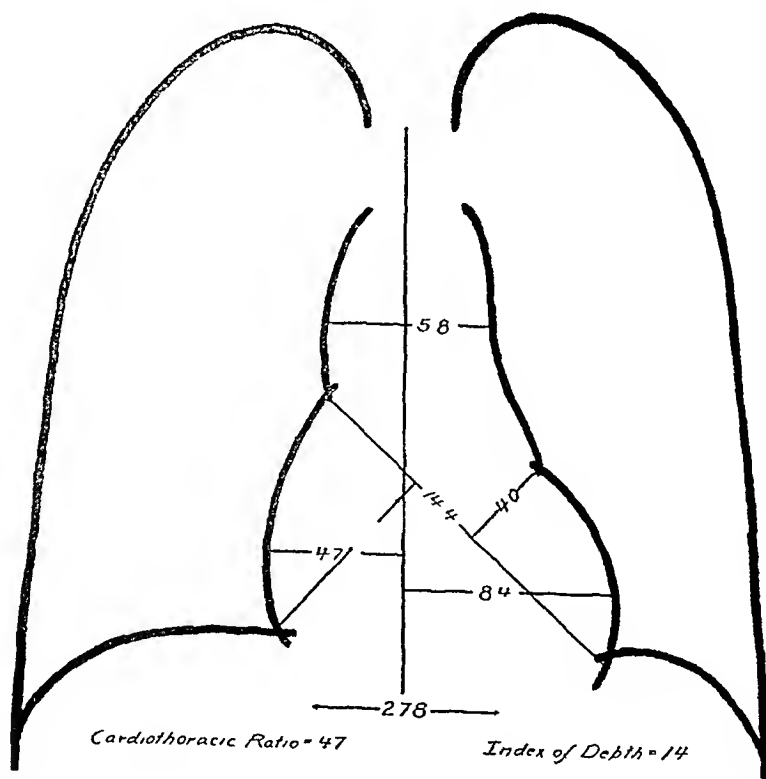


Fig 11—Normal subject Dr W A , aged 27, weight, 145 pounds, height, 69 inches

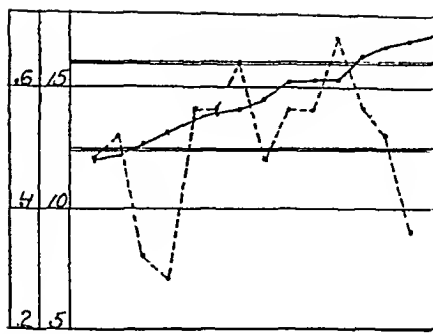


Fig 12 — Mitral stenosis, predominant valvular lesion, markedly increased cardiothoracic ratio, but normal index. Ordinates represent index and cardiothoracic ratio as explained in Figure 4. Index, broken line, plotted against cardiothoracic ratio solid line. Abscissa, each square a case. Horizontal solid lines, upper normal limits for each measurement.

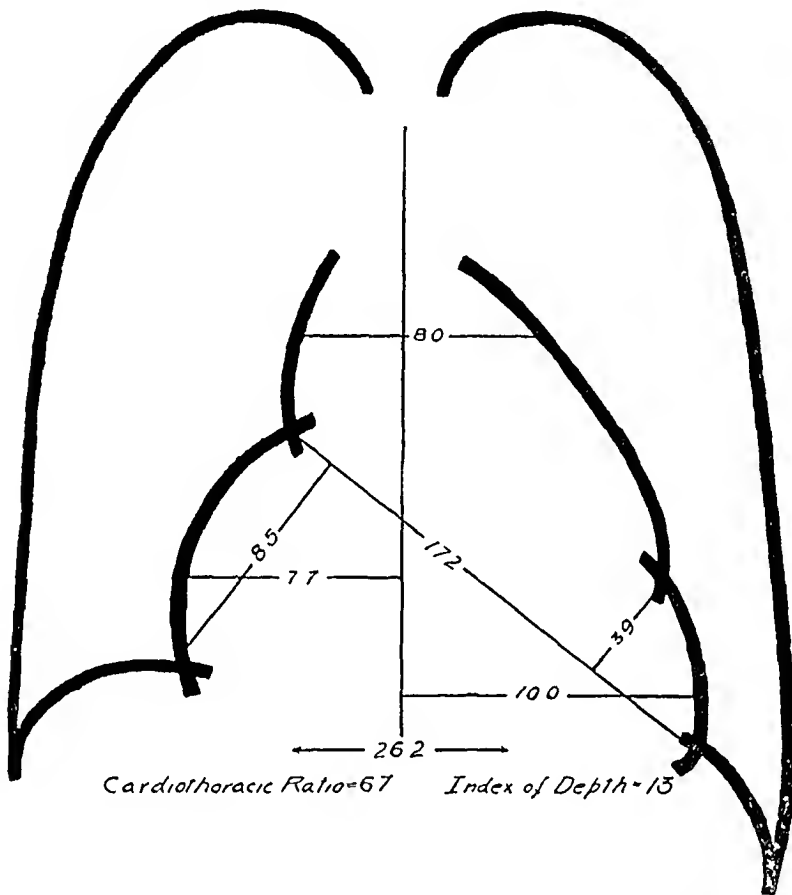


Fig 13 — Rheumatic heart disease with mitral stenosis, predominant valvular lesion, increased cardiothoracic ratio and index. Roentgen ray 82669, House, West Med No 248317. Weight, 108 pounds, height, 62 inches. A white woman, 35 years of age, sitting propped up in bed with evident moderate respiratory embarrassment. Had scarlet fever at 8 years of age, with "rheumatism" the following year and frequent tonsillitis. For the past two years has had dyspnea, palpitation and pains all over the body on exertion, which have been increasing in severity. Has an unproductive cough which keeps her awake nights. Examination shows a loud systolic apical murmur, obscuring the first sound and transmitted to the axilla, at the apex is also heard a short mid-diastolic murmur. Sounds are absolutely irregular, slightly rapid and of forcible quality. Blood pressure, 110/70. Scattered musical, sticky râles over both lungs anteriorly and posteriorly. The liver edge is felt 4 cm below the right costal margin. Scars on the right shin. Blood Wassermann. Strongly positive Electrocardiograph. Auricular fibrillation (coarse), rate, 70, diphasic T. Roentgen ray shows marked prominence of the right and left auricular arcs and pulmonary arc. The left ventricular arc is flattened, apex pointed and displaced downward. In general, heart is "acorn-shaped." In the right antero-oblique position, there is marked prominence in the region of the auricles. Cardiothoracic ratio = 0.67, index of depth = 13 mm. Findings suggest marked enlargement of the heart, confined to the auricles and right ventricle. The chest plate in addition shows moderate prominence and thickening of the larger lung markings throughout both lung fields. Diagnosis: Rheumatic heart disease, with mitral stenosis, auricular fibrillation and failure of the congestive type.

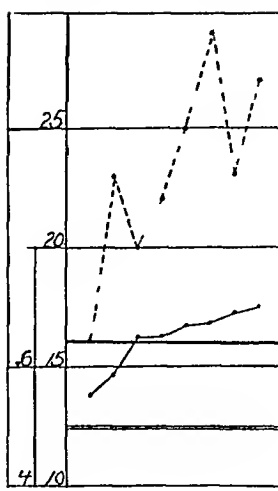


Fig 14—Mitral and aortic disease Legend same as in Figure 12

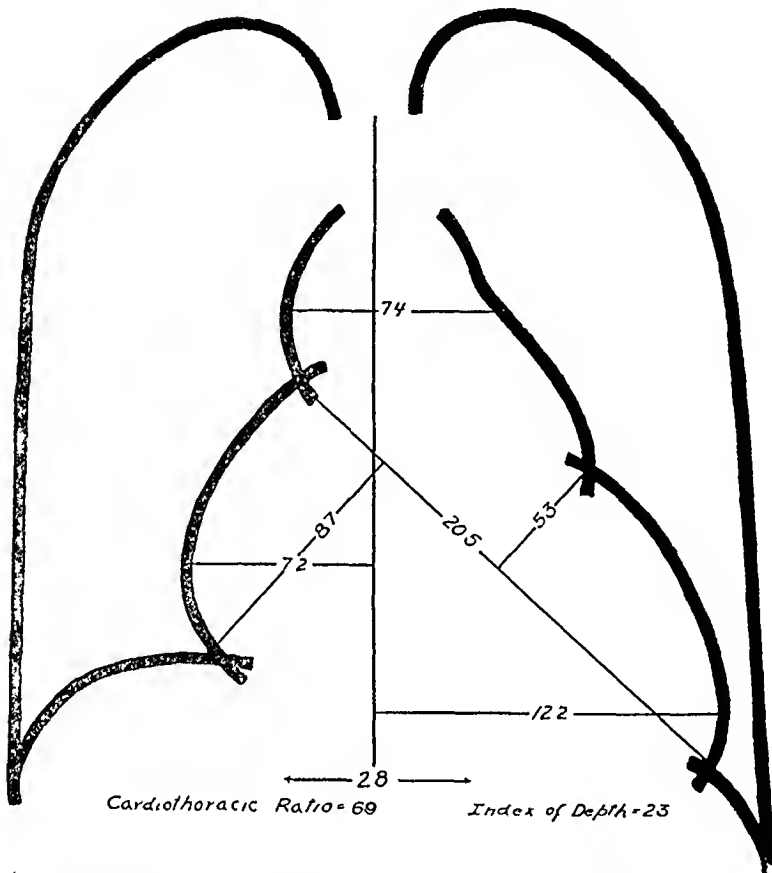


Fig 15—Rheumatic heart disease with mitral stenosis and regurgitation, and aortic regurgitation Roentgen ray 78826, House, East Med No 245036 Weight, 145 pounds, height, 72 inches A white man, 20 years of age, sitting propped up in bed, showing slight cyanosis of the lips, and noddling of the head, with each systolic pulsation of the great vessels in the neck Had diphtheria in childhood For the past seven years, has suffered from attacks of articular rheumatism accompanied by tachycardia Attacks of tachycardia have increased in frequency and severity Had a severe attack on admission, with a pulse of 175 Has slight dyspnea on exertion Examination shows a muffled and distant first sound with systolic murmur transmitted to the axilla, followed by a diastolic transmitted to the base Diastolic at the aortic area, loudest over left sternal border, occasional extrasystole Capillary pulse and pistolshot sound over the femoral artery Blood pressure 160/40 Electrocardiograph Left ventricular preponderance, slurring of R in Lead II, rate 120 Blood Wassermann Negative The roentgen ray shows a general enlargement of the heart shadow, prominence of the right and left auricular, and left ventricular arcs The apex is displaced to the left and slightly downward In the right antero-oblique position there is marked prominence in the region of the auricles Cardiothoracic ratio = 0.69, index of depth = 23 mm Findings suggest general enlargement of all the heart cavities Diagnosis Rheumatic heart disease with mitral stenosis and regurgitation, and aortic regurgitation (with no failure)

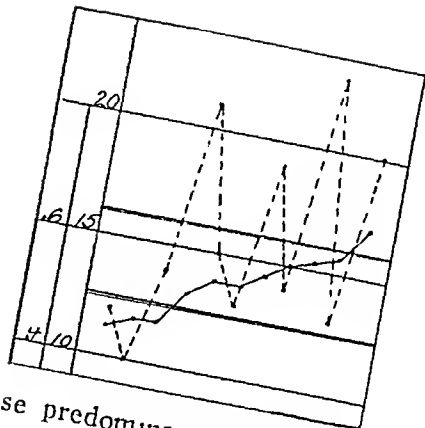


Fig 16—Aortic disease predominant Legend same as in Figure 12

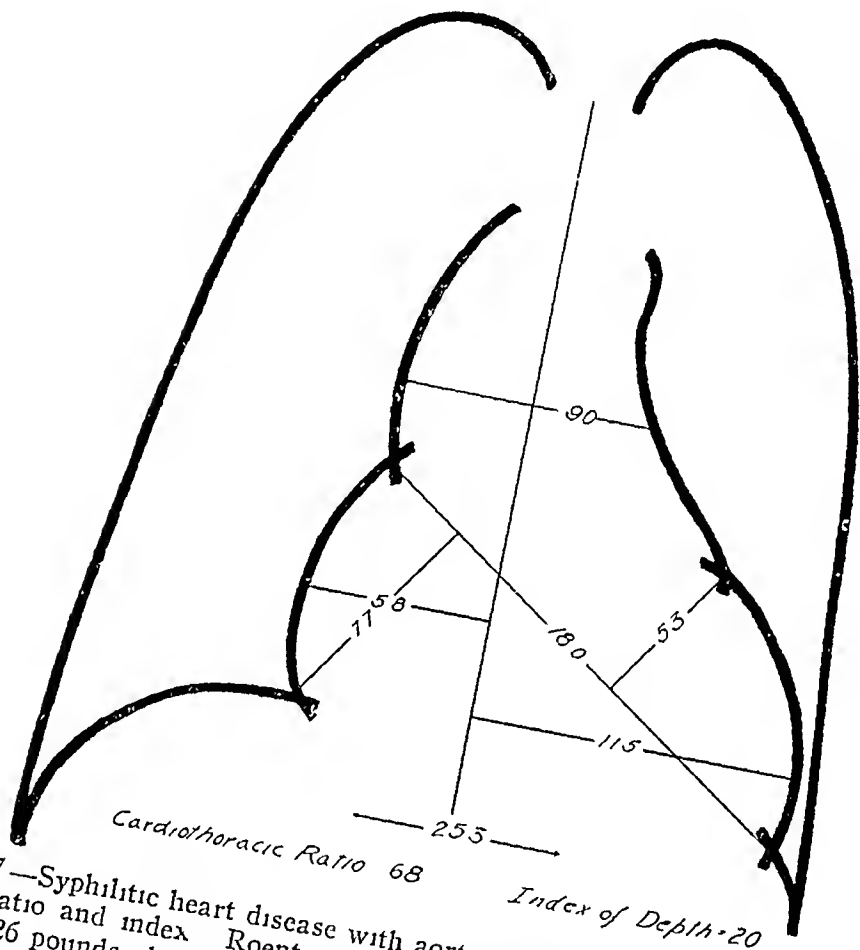


Fig 17—Syphilitic heart disease with aortic regurgitation, increased cardiothoracic ratio and index. Roentgen ray 82949, House, East Med No 248495. Weight, 126 pounds, height, 66 inches. A rather thin, pale-looking white man, club valet, aged 38, without any history of previous cardiac disturbances. Comes to the hospital for relief of palpitation (difficulty felt in climbing stairs), and insomnia since six months ago, which have become exaggerated in the last two weeks. Examination shows the right pupil greater than the left, both regular in outline, but react very sluggishly to light, and well in accommodation. Loud systolic and a very short diastolic murmur at the apex, loud, rough systolic and short diastolic at the base. Blood pressure 140/20. Blood Wassermann Strongly positive at two examinations. The roentgen ray shows a marked increase in the shadow of the heart to the left with moderate convexity of the left ventricular arc, and lowered, rounded apex, without prominence of the auricular arcs. In general, heart has the "lying egg-shaped" appearance. The supracardiac shadow is moderately increased in the anteroposterior and right antero-oblique positions. In the latter position, there is no prominence in the region of the auricles. Cardiothoracic ratio = 0.68, index of depth = 20 mm. Findings suggest moderate dilatation of the aorta and enlargement of the heart in the region of the left ventricle. Diagnosis Syphilitic heart disease with aortitis, moderate dilatation of the ascending aorta, aortic regurgitation and left ventricular preponderance.

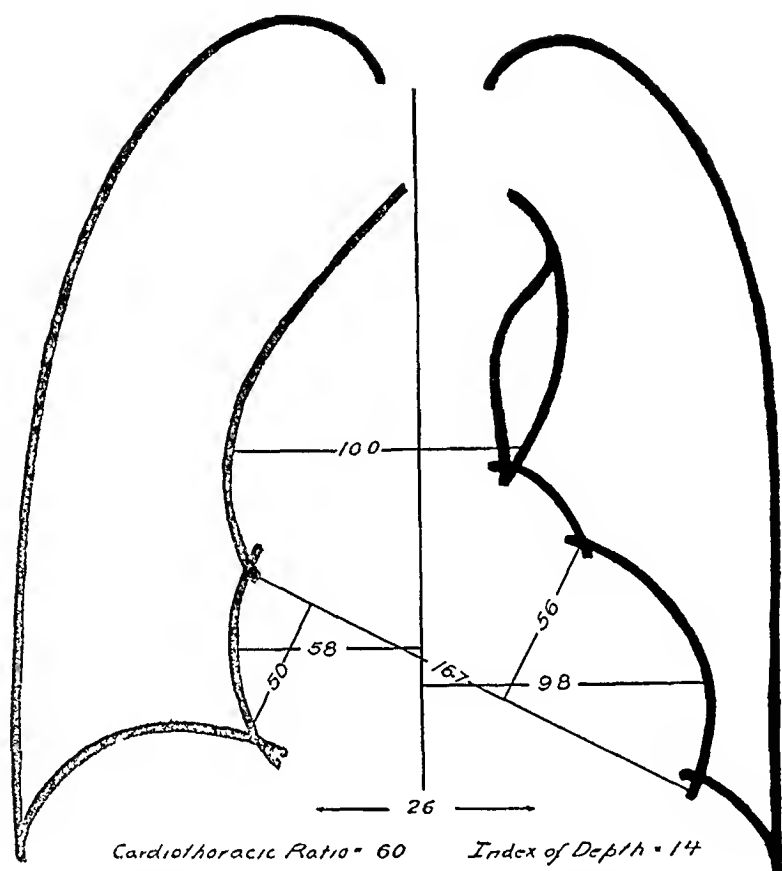


Fig 18—Syphilitic heart disease with aortic regurgitation, increased cardiothoracic ratio but normal index. Roentgen ray 80130, Outpatient Department No 408054. Weight, 136 pounds, height, 67 inches. A white fairly well developed man, 45 years of age, who has had an unproductive cough and sharp pains in the right shoulder for the last three weeks. Examination shows pupils which react sluggishly to light but well in accommodation. Systolic and diastolic murmurs at the apex. The latter is loudest over the aortic area. Blood pressure 210/80. Blood Wassermann strongly positive at three examinations. The roentgen ray shows an increase in the shadow of the heart to the left, with moderate prominence of the left ventricular and rounded apex, without prominence of the auricular arcs. In general, heart has a slightly "lying egg-shaped" appearance. There is a marked increase in width of the supracardiac shadow to the right and left, particularly to the right at the base, and tortuosity of the aorta with a prominent knob. In the right antero-oblique position, the base of the supracardiac shadow is slightly increased. There is no prominence in the region of the auricles in this position. Cardiothoracic ratio = 0.60, index of depth = 14. Findings suggest slight dilatation and arteriosclerosis of the ascending aorta, and enlargement of the heart in the region of the left ventricle. Diagnosis: Syphilitic heart disease with aortitis, slight dilatation and arteriosclerosis of the ascending aorta, and aortic regurgitation.

right and left ventricles. It is well to bear this order in mind for a comparison with the index findings charted in these same affections later on.

Figure 10, which shows the ratio of the weight of the left ventricle to that of the right, is charted because of its interest from an electrocardiographic standpoint and may offer a basis for future comparison with the index measurement.

Let us now consider the index measurement in these various affections and its relation to the cardiothoracic ratio. It is observed in predominant mitral stenotic lesions (Fig 12) that while the cardiothoracic ratio is generally increased, the index measurement remains practically normal. Figure 13 is an illustrative case of this group, in

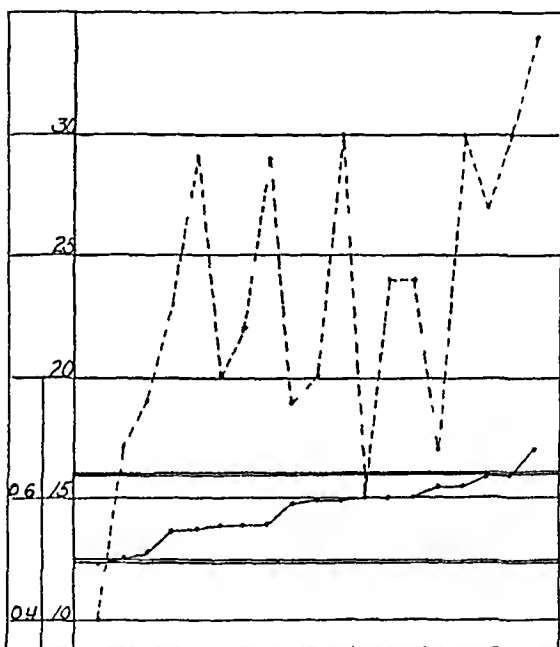


Fig 19—Hypertensive heart disease with and without clinical evidence of chronic nephritis, systolic blood pressure 160 mm or more, diastolic 100 mm or more. Legend same as in Figure 12.

which the marked increase in transverse width is noted with a comparatively small index. On the other hand, when there is an accompanying aortic lesion, there is a general concomitant increase in index with the cardiothoracic ratio as shown in Figure 14 and illustrated in Figure 15. When we come to the cases of aortic regurgitation (Fig 16) a marked lack of harmony is noted between the index and cardiothoracic ratio. Figure 17 illustrates a case of syphilitic heart disease with aortic regurgitation, having an increased cardiothoracic ratio and an increased index measurement, while Figure 18 shows a heart in the same type of disease, with an increased ratio and a normal index. In this connection, it will be recalled, under theoretic considerations of



Figure 1, that considerable enlargement of the left ventricle can exist posteriorly and still exert no influence on the index measurement. In hypertensive heart disease, with and without clinical evidence of nephritis (Fig 19), there is, in general, an increased index when the cardiothoracic ratio is increased, except in one or two instances in which the former is slightly increased or normal when the latter is markedly above normal. Figure 20 illustrates a case of hypertensive heart disease (with chronic nephritis) with an increased cardiothoracic ratio and index of depth. Figure 21, a case of the same group, shows an increased

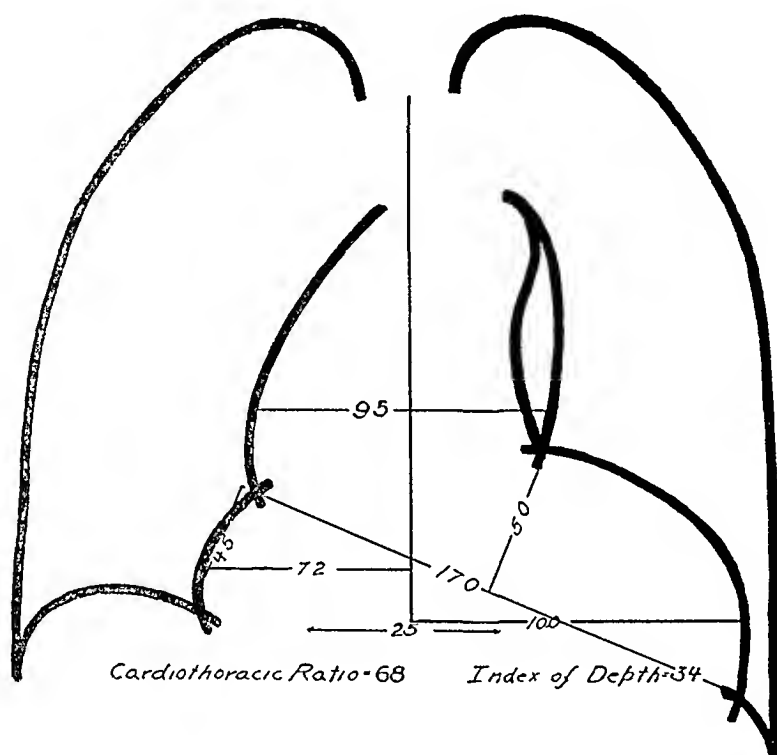


Fig 20 — Hypertensive heart disease, increased cardiothoracic ratio and index. Roentgen ray 78888, House, East Med No 245881. Weight, 187 pounds, height, 70 inches. A white, well developed woman, 55 years of age, who for a number of years has suffered from frequent headaches, transient attacks of dizziness, nocturia, dyspnea on exertion, and occasional attacks of palpitation with stabbing precordial pain. Examination shows heart sounds of good quality, loud, A<sub>2</sub>, first sound short and snappy at the apex. Blood pressure 235/140. Slight edema of the ankles. Fundi show albuminuric retinitis. Urine shows a trace of albumin, specific gravity 1.014, occasional hyaline cast. Blood nonprotein nitrogen 45.6 mg per 100 cc. The roentgen ray shows marked increase in the heart shadow to the left, exaggeration of the left ventricular convexity, and apex blunted and elevated. No prominence of the auricular arcs. In general, heart is "goose-shaped." The supracardiac shadow measurement is increased in width in the anteroposterior and right antero-oblique positions, aortic shadow tortuous with a prominent knob, but diaphragmatic shadows are high. In the oblique position, there is no prominence in the region of the auricles. Cardiothoracic ratio = 0.68, index of depth = 34 mm. Findings suggest marked enlargement of the left ventricle. Diagnosis: Hypertensive heart disease, with chronic nephritis, arteriosclerosis of the aorta, and left ventricular preponderance.

cardiothoracic ratio and a normal index measurement. There are sufficient grounds, however, in the latter case to substantiate arguments for and against any considerable enlargement in depth. It is shown because of the possibility of enlargement in depth of the left ventricle with a normal index, and to be borne in mind in connection with similar measurements in aortic disease.

Let us now compare the index measurement in these various cardiac affections with the figures of Lewis for ventricular weights, to see whether harmony exists, and, if not, to seek some plausible explanation for the discrepancy. Figure 22, in which the indices are charted, shows the order of progression to be as follows: normal and mitral stenosis,

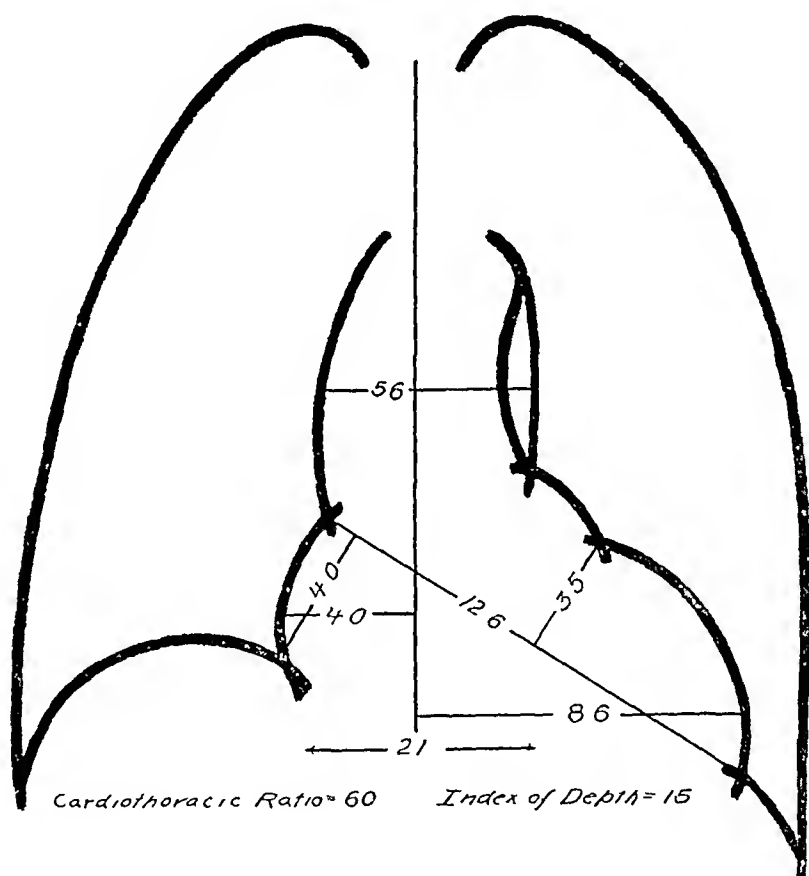


Fig 21—Hypertensive heart disease, increased cardiothoracic ratio, but normal index. Roentgen ray 79989, Outpatient Department No 385516. Weight, 140 pounds, height, 63 inches. An obese, white woman, 59 years of age, who for the last two years has suffered from severe attacks of anginal (?) pain. She had diphtheria twice during childhood. Examination shows heart sounds of good quality, and a short systolic at the apex. Blood pressure 220/120. Slight edema of the shins. Electrocardiograph: Tachycardia (? paroxysmal—? sino-auricular) with intraventricular block of left bundle branch type. Rate, 140. The roentgen ray shows an enlargement of the heart shadow to the left, accentuation of the left ventricular convexity and blunting of the apex. There is no prominence in the region of the auricles in the anteroposterior or oblique positions. Cardiothoracic ratio = 0.60, index of depth = 15 mm. Findings suggest enlargement of the left ventricle. Diagnosis: Hypertensive heart disease, chronic nephritis (?) and failure of the anginal type (?).

aortic regurgitation, aortic and mitral disease, and finally hypertensive heart disease, in which the highest figures are obtained. Note that this order is quite different from that observed in Figure 8, for the weights of the left ventricle, where the hearts with aortic regurgitation were the heaviest.

A study of the measurements charted in Figure 22, and of the illustrations of the characteristic examples of these various cardiac affections, suggests a plausible explanation for this apparent discrepancy. It will be noted that in cardiac affections in which mitral stenosis is the predominant valvular lesion, the enlargement of the heart is virtually wholly on the right side, while the left ventricle is

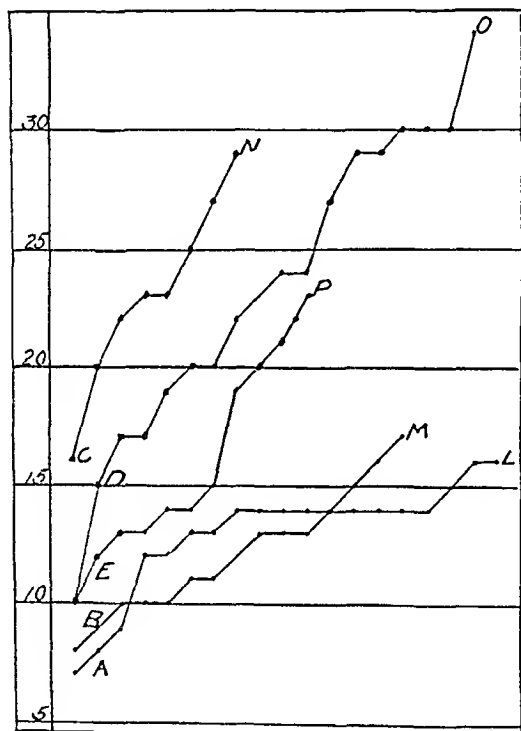


Fig 22—Indices of depth in normal and pathologic subjects. Ordinate, index in mm, otherwise legend the same as in Figure 8, weights of the left ventricle, with which it should be compared.

comparatively small or normal in size, but the left ventricular outline or arc is markedly flattened, the apex is pointed and displaced downward, in general the heart is "acorn-shaped," and here the index measurement is small or normal. It will be recalled, also, that the normal vertical shaped hearts give the smallest index measurements.

In aortic and mitral disease, the heart is enlarged both to the right and left, the left ventricular arc is moderately exaggerated, the apex is rounded, displaced to the left, and slightly raised, and here the index is increased.

In pure aortic valvular disease, with regurgitation predominating, the left ventricle is generally enlarged, the exaggeration of the left ventricular arc varies, but the apex is displaced downward, giving the heart a "lying egg shaped" appearance, in other words, producing most of the prominence or bulge posteriorly close to the spine, and thus the enlarged portion of the left ventricle may or may not be placed outside of the path of the oblique rays, thereby making the index measurement variable

In hypertensive heart disease, the enlargement is confined in great measure to the left ventricle, the left ventricular arc is markedly exaggerated, the apex is rounded or blunted and displaced upward, giving the heart a "goose shaped" appearance or the heart "en sabot" of the French, and here the index is generally enlarged, at times quite markedly. These observations suggest that the most important factor influencing the index of depth is the shape of the left ventricle

#### SUMMARY AND CONCLUSIONS

The technic of Bordet and Vaquez for obtaining the "index of depth" and the "angle of disappearance of the apex" is described

From theoretic considerations of anatomic charts, and observations on nine anatomic cross sections of the trunk in the apical region of the heart, nineteen normal, and fifty-one pathologic subjects, the following conclusions, tentative to necropsy verification, are suggested

1 There is no harmony between the index of depth and the angle of disappearance of the apex

2 There are normal cases in which the angle exceeds quite definitely the upper normal limit (40 degrees) of Bordet and Vaquez

3 Normally the index does not exceed 16 mm

4 There are undoubtedly cases of enlargement of the left ventricle in depth with a normal index

5 It is quite obvious from the above findings that the index is of value only in a positive direction

6 The most important factor influencing the index measurement is the shape of the left ventricle

7 When from the anteroposterior fluoroscopic or plate examination it is difficult to differentiate between a heart with an aortic valvular lesion and one with hypertensive disease, an index measurement of 25 mm or more is very suggestive of the latter affection

8 The index may be a very valuable additional method for studying the progress of hypertrophy of the left ventricle in an individual case

In conclusion it is well to recall the words of Alfred Cohn<sup>9</sup> "No phase of the phenomena associated in maintaining the circulation may

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<sup>9</sup> Cohn, A. E. Nelson Loose Leaf Medicine, Diseases of Circulatory System, New York 4 175, 1920

be neglected, nor in the clinic may any intensification of study designed to widen the range of knowledge be omitted "

For constant help and invaluable suggestions throughout this work, I wish to express my appreciation to my chief, Dr George W Holmes, also to Drs Paul D White<sup>10</sup> and Louis E Viko of the cardiographic laboratory, for clinical aid

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<sup>10</sup> White, P D, and Meyers, M M The Classification of Cardiac Diagnosis, J A M A **77** 1414 (Oct 29) 1921

# PATHOLOGIC PHYSIOLOGY OF POLYCYTHEMIA VERA \*

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CINCINNATI

Some features of the abnormal physiology of polycythemia vera (Vaquez or Osler's disease) were studied in a case in the medical wards of the Cincinnati General Hospital, on the service of Dr Mark Brown

## REPORT OF CASE

*History*—The patient (No F 9928), a well developed man of 62, was in good health until five years ago. While on duty as a policeman, he was struck in the abdomen with an iron bar. One-half hour later he became weak and helpless and was taken to a hospital. The following day the abdomen was opened and the peritoneal cavity was found to be full of blood from a ruptured mesenteric artery. His recovery was uneventful, and he continued in fair health with occasional attacks of vertigo and headache. Some of his symptoms at that time led to a tentative diagnosis of tuberculous meningitis, but there was apparently nothing to substantiate this. He noted that his symptoms were always definitely aggravated by two things—the use of tobacco and certain foods (onions). Seven months later, he accidentally struck his left side against some obstruction. A severe pain developed, and soon afterward he noticed that there was a mass in the left upper quadrant of his abdomen. It was "hard as a rock" at first but later became smaller and softer.

About one and a half years after he had noticed the enlarged spleen, he began to suffer from severe pain in his toes and fingers, later extending to the feet and hands. He said that he felt as if they had been "smashed with a hammer" and "the blood was under tremendous pressure inside." He obtained some relief from the pain by holding his hands above his head. The discomfort was not as great in summer as in winter.

*Physical Examination*—Among the essential features on physical examination were the flushed appearance of the face and neck, which were reddish purple in color, and the congestion and cyanosis of the hands, nail beds, feet, sclera, tongue and pharynx. His voice was high pitched. His teeth had all been removed years ago. The tonsils were small. In the chest, a few, fine crepitant râles were heard at the end of deep inspiration in each axilla and both bases.

The spleen was hard, smooth and readily palpable 14 cm below the left lower costal border. The enlargement was also demonstrable by the roentgen ray. On percussion, the total length was 36 cm, and the width 12 cm. No enlarged lymph glands were noted. The heart was normal in size. The weight at the time of the first examination was 164 pounds, increasing during the course of three months to 170 pounds. The patient noted that he did not sweat much.

*Blood Examination*—The red and white cells were counted many times with results as shown in Table 1.

The count of Jan 21 1922, followed three days after roentgen-ray treatment over the splenic region and was made with a U S Bureau of Standards certified pipet and hemocytometer slide. June 6, 1922, the hemoglobin (Sahli)

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\*From the Department of Medicine of the University of Cincinnati and the Cincinnati General Hospital

reading was 180 per cent, and the hemoglobin calculated from the iron content was 193.6 per cent (using 16,693 as the molecular weight of hemoglobin). The color index varied from 0.97 to 0.88 according to the methods used for hemoglobin estimation. The hemoglobin calculated from the oxygen combining power (Van Slyke method) was from 163.6 to 170.8 per cent. This corresponded to 30.07 cc and 31.61 cc of oxygen bound by 100 cc of blood.

A study of the blood made by Dr. Roger S. Morris showed 81.3 per cent polymorphonuclear neutrophils, 9.3 per cent lymphocytes, 2 per cent eosinophils, 4.3 per cent transitionals and large mononuclears and 1.5 per cent mast cells, in 736 cells. No myelocytes were noted at this examination. Two normoblasts were encountered. The red cells were essentially normal in appearance. A count made subsequently showed 1 eosinophilic myelocyte and 4 normoblasts to 600 leukocytes which corresponded to 120 nucleated red cells per cmm (May 23, 1922).

*Spectroscopic examination* of the blood showed the normal absorption bands. Hematin crystals formed by heating the blood with glacial acetic acid and sodium chlorid showed no abnormalities.

The platelet count was 200,000 (Wright and Kinnicutt method). The bleeding time was  $1\frac{1}{4}$  minutes, and the coagulation time (capillary tube method) was longer than twenty-three minutes.

TABLE 1—RESULTS OF THE BLOOD CELL COUNT

Date	Erythrocytes	Leukoocytes
4/ 9/20	7,360,000	8,274
10/ 4/21	7,480,000	
1/13/22	10,950,000	11,600
1/14/22	13,200,000	14,300
1/21/22	15,910,000	21,000
1/22/22, p m	13,420,000	13,600
n m	9,904,000	
1/23/22	12,000,000	11,700
1/24/22	10,208,000	9,203
1/29/22	8,680,000	11,850
2/ 6/22	9,312,000	
5/15/22	9,024,000	
5/23/22	9,136,000	14,000
6/ 6/22	9,240,000	16,500
6/20/22	9,640,000	14,250

The corpuscles were more resistant than normally to hypotonic salt solutions, hemolysis beginning at 0.3 per cent and reaching completion at 0.2 per cent. Some of the patient's blood was used in a transfusion to a pernicious anemia patient. The color index of the recipient returned to normal at the end of three days, the most common time being two days in the average transfusion. The corpuscle volume was 2.4 times that of a normal blood of 5,000,000 red cells on Jan. 23, 1922, when the count was 12,000,000. The plasma was a deep yellowish red.

The blood Wassermann reaction was repeatedly negative. The viscosity of the blood (Ostwald viscosimeter) was increased to 12.27 times that of water at 28.5 degrees which would correspond to 11.3 at body temperature (38 C) being over twice normal (from 4.73 to 5.89). The surface tension was reduced. Specific gravity, 1.078 (by weighing).

*Chemical analysis* of the blood (determined by Miss Agnes Wolfstein) showed 0.079 per cent sugar (Folin and Wu method), 15.7 mg urea, 6.9 mg uric acid (Folin and Wu method). A uric acid determination three months later showed 8.59 mg (Benedict method). Another determination showed 95 per cent more in the plasma than in the corpuscles. The blood chlorids were 150 mg. Blood cholesterol (determined by Dr. Shiro Tashiro) was from 0.112 to 0.176 mg per 100 cc and bile salts were normal. Iron (M. L. Isaacs), 90 mg per 100 cc (Brown's method, normal, from 42 to 52 mg).

*Blood Pressure*—This remained around 125 systolic, 85 diastolic.

*Urine*—The urine was essentially negative. A very slight trace of urobilin was found on one occasion, but subsequently it was negative. The phenol-sulphonephthalein output was from 37 to 50 per cent in two hours (not catheterized).

*Metabolism Determinations*—The relation between the oxygen intake (basal metabolic rate) as determined on the Sanborn-Benedict apparatus, the respiration rate, the heart rate, the red count and the vital capacity is shown in Table 2 (Corresponding observations taken at the same time)

TABLE 2—RESULTS OF METABOLISM STUDIES

	Jan 15, 1922	Feb 3, 1922	May 15, 1922	May 23, 1922	June 6, 1922
Rate of oxygen intake (basal conditions)	+12%	+38.7%	+37.9%	+34.5%	+33.8%
Respiratory rate	12	16	16	16	12
Pulse rate	68	64	76	68	75
Red count			9,024,000	9,136,000	9,240,000
Vital capacity (V. O.)	2,494 c c	1,398 c c	2,123 c c	2,281 c c	2,277 c c
Calculated V. O. (Meyers <sup>1</sup> )	4,659 c c	4,659 c c	4,782 c c	4,782 c c	4,742 c c
V. O., per cent of calculated	53.5%	30.0%	44.39%	51.89%	48.01%
Temperature	97.6 F	97.8 F	98.0 F	97.4 F	97.8 F

The average volume of air breathed per minute (reduced to 0 C and 760 mm pressure) was 11,825 c c (May 23, 1922) under basal conditions. The daily temperature varied from normal to slightly subnormal, with an occasional rise to 99 F. The vital capacity was slightly greater in sitting position, than while lying down (June 6, 1922, sitting, 2,590, lying down, 2,277). In the sitting posture, the vital capacity was 54.62 per cent of the calculated.

June 20, 1922, the oxygen content of the venous blood was 27.23 c c of oxygen per 100 c c of blood. With a total oxygen combining capacity of 31.61 c c per 100 c c of blood, this was 86.12 per cent saturated. The carbon dioxide combining power of the plasma (Van Slyke method) was 43.5 c c per 100 c c of blood.

#### DISCUSSION

This case presents most of the classical symptoms and signs of erythremia. The history of an abdominal injury is interesting, as some of the symptoms appeared to have been first noticed from that occurrence. The etiologic relation is, of course, problematical.

The high red count reached on Jan 21, 1922, followed a treatment of the spleen by exposure to the roentgen rays, and may have been stimulated by it (inhibition of macrophages?). The counts of the preceding days, however, showed a tendency to rise before the treatment was started. The rise of the leukocyte count with that of the red cells suggests that a concentration effect of the corpuscles and plasma was a significant factor in the variation in the number of corpuscles in the peripheral circulation from day to day. The blood counts extending over a period of three years showed a persistent polycythemia.

The question of the mechanism of the increased number of red cells may find a solution in two factors, increased production (nucleated red cells in the peripheral circulation) and decreased destruction (high resistance to hemolysis in hypotonic solutions). The protective, anti-

<sup>1</sup> Meyers, J. A. Studies on the Respiratory Organs in Health and Disease, Jour.-Lancet 41 252, 1921



hemolyzing action which cholesterol exerts on red cells was not increased, as the values were normal or below normal

The increased uric acid in the blood (6.9 and 8.59 mg.), in the absence of renal involvement, may have its origin in the liberated nuclear material formed in the increased production of red cells, from the extrusion or dissolution of the nuclear material of the normoblasts at their place of origin. The normoblasts in the circulation are of importance in this connection and suggest that there is an abnormal stimulus to the formation and circulation of the red cells. This is suggestive of a normal endogenous source of uric acid in the body during health. A high uric acid content of the blood in some stages of leukemia has been attributed to the nuclei and nuclear metabolites of the white cells, but the "discarded" nuclei of the red cells may also be a factor. The high uric acid content of the blood in pernicious anemia (Gettler and Lindemann<sup>2</sup>) is compatible with this view. Erickson<sup>3</sup> and others have reported an increase in the blood uric acid in polycythemia vera. Fitz<sup>4</sup> noted that while the total nonprotein nitrogen, fat, uric acid, and iron per 100 cc of whole blood are definitely increased and the sugar concentration slightly above normal these substances may be in approximately normal concentration in the plasma. Because of the bulk of corpuscles, he does not consider the findings for whole blood necessarily pathological. Theis and Benedict,<sup>5</sup> however, in studies on blood in different diseases, noted that in only eight cases out of 104, the uric acid concentration was greater in the corpuscles than in the plasma. In the other ninety-six cases the concentration was similar in both corpuscles and plasma, or greater in the plasma. If a similar relationship holds constantly in erythremia, as in the present case, there is an absolute increase in the uric acid, and especially, as in this case, the other blood constituents were not increased. Rouzand and Thiery<sup>6</sup> noted that when there is a decreased blood viscosity, there is comparatively more uric acid in the serum than in the whole blood, and when the viscosity is greater, the conditions are reversed. This was not true in the present case, however. It is interesting to note that a persistent headache was relieved fairly quickly following the taking of phenylcinchomonic acid, 0.5 gm., three times a day.

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2 Gettler, A. O. and Lindemann, E. Blood Chemistry of Pernicious Anemia, *Arch Int Med* **26** 453 (Oct.) 1920

3 Erickson, R. J. A Case of Vaquez Disease, *Canad M A J* **7** 817 (Sept.) 1917

4 Fitz, R. Polycythemia, *Oxford Med* **2** 769, 1920

5 Theis, R. C., and Benedict, S. R. Distribution of Uric Acid in the Blood, *J Lab & Clin M* **6** 680 (Sept.) 1921

6 Rouzand and Thiery. Relation entre la viscosité sanguine et la répartition de l'acide urique dans le serum et dans le sang total, *Compt rend Soc de Biol* **85** 962 (Nov.) 1921

The apparent increase in coagulation time was evidently due to the relative diminution of the fibrin element and the increase in the corpuscular element in a given unit of clot

The lowered vital capacity (from 30 to 53 per cent of the calculated normal) may have been dependent, to some extent, on the mechanical congestion and engorgement of the pulmonary capillaries. The crackling râles heard were not incompatible with this. A similar congestion in the legs gave rise to ulcers which suggested areas of thrombosis or infarction.

The increased oxygen supply to each part was evidently the factor which compensated for the flow of a highly viscous liquid under low pressure, and prevented the development of edema which frequently results from similar mechanical conditions. Localized edema sometimes developed after prolonged exertion. The viscosity at body temperature was 11.3 times that of water or from 1.92 to 2.39 times the normal limits for blood, at a time when the cell count was from 1.85 to 2.05 times normal limits. The viscosity is thus coordinate with the red cell count. The viscosity was also increased by the comparatively low body temperature of 97 and 98 F (mouth). A decrease of 5 degrees in temperature may increase the viscosity 4 per cent (Mathews<sup>7</sup>). On cooling the patient's blood to 12.5 degrees, the mass became too thick to flow but the fluidity was restored on warming to room temperature. In the hands and feet, the surface blood was exposed to temperature considerably below this (from 5 to 10 degrees), varying with the outside temperature may increase the viscosity 4 per cent (Mathews<sup>7</sup>). On two clinical phenomena—pain in the hands and feet, and aggravation of the symptoms in cold weather. The pain was partially relieved by elevating the hands or the feet. Lyon<sup>8</sup> notes a parallelism between the viscosity of the blood and the blood pressure up to middle life (from 30 to 39 years), but after this the agreement ceases. The viscosity is then parallel to the hemoglobin and red cell count and falls as the blood pressure rises with age. In this case while the viscosity was increased with the cell count, the blood pressure was low for the age of the patient, with no marked increase during the course of two years. The absence of myocardial hypertrophy in this case, and as noted by Weber,<sup>9</sup> is an odd feature of the disease under these conditions.

Two factors served to compensate for the reduced vital capacity. First, the increased hemoglobin with a comparatively normal oxygen

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7 Mathews, A. P. *Physiological Chemistry*, 1921, Ed. 3, p. 512.

8 Lyon, D. M. *Blood Viscosity and Blood Pressure*, *Quart. J. M.* **14** 398 (July) 1921.

9 Weber, P. *Polycythemia*, Allbutt and Rolleston's System, London **5** 831, 1909.

combining power, and, second, the greatly increased minute volume (from 9,711.6 to 11,825 cc) of air breathed, practically about twice normal. This latter is interesting as the respiration rate was not increased, but the tidal volume was increased from 32.4 to 35.5 per cent of the vital capacity during quiet breathing, instead of from 7 to 10 per cent, the calculated normal.

The increase in the rate of oxygen consumption (basal metabolic rate) remained from 31 to 38 per cent above normal during a period of observation of five months. An increase has been reported as being characteristic of erythremia, just as in the leukemias and pernicious anemia. The increase was present with a pulse rate of from 64 to 68, and a respiration rate of from 12 to 16, differing from the hyperthyroid types.

The basal metabolic rate, assuming that the respiratory quotient is not abnormal,<sup>10</sup> is more parallel to the blood destruction or possibly nuclear destruction, than to the number of cells in the circulation at the time. The increased number of cells destroyed, even in the presence of a normal or moderately reduced rate of destruction, makes the condition somewhat similar to the destructive anemias, where the rate is also high. If blood destruction went on at a normal rate, there were practically twice the number of cells to be destroyed. In erythremia, as well as in some stages of the leukemias and pernicious anemias, besides the increase in basal metabolic rate, the blood uric acid is high. In the leukemias this has been given as an evidence of leukocyte activity. In erythremia, however, the leukocytes are not increased in comparable ratio. The nuclei from the maturing normoblasts in the bone marrow give a source which must be considered.

The reddish cyanotic appearance is apparently not directly associated with the increase in red cells, as in cases of anerythremic erythremia described by Morris<sup>11</sup> the cyanosis was present, but the red cell count was not increased. Christian<sup>12</sup> noted in five cases of polycythemia in a series of ten, that the deep color was not always pronounced, and some of the patients appeared to be pale. There was no relation in the present case between the depth of color of the face and extremities and the daily variation in the blood count. One factor, as noted by Osler<sup>13</sup> appeared to be the state of the capillaries. Examination of

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10 The average respiratory quotient of four cases studied by Senator (Ueber Erythrozytosis [Polyzythemia rubra] megalosplenica), *Ztschr f klin Med* 60 360, 1906) was 0.816.

11 Morris, R. S. Anerythremic-Erythremia, *Bull Johns Hopkins Hosp* 21 37 (Feb) 1910.

12 Christian, H. A. Nervous Symptoms of Polycythemia Vera, *Am J M Sc* 154 547 (Oct) 1917.

13 Osler, W. Chronic Cyanosis with Polycythemia and Enlarged Spleen, *Am J M Sc* 126 187 (Aug) 1903.

the capillary loops at the base of the nail beds (using olive oil to clear the skin, and using the 10 ocular and  $\frac{2}{3}$  objective in the microscope) showed that one limb and the arch of most of the loops was wide and distended, while the other limb was comparatively narrow. On other occasions both loops were distended. On "frosting" the surface with a stream of ethyl chloride, the capillaries became greatly distended, but as the temperature returned to normal, they became relatively narrow and pale for a time, gradually returning to their original condition. In a few spots distension remained and there appeared to be a practical thrombosis. The lowering of the temperature increases the viscosity beyond the stage of fluidity, as demonstrated *in vitro*, and stagnation and dilatation take place. The subsequent narrowing of the vessels appears to have been brought about by a nervous mechanism. The depth of color in the skin is due in part, at least, to the state of distention of the capillaries.

The hemoglobin appeared to be normal in all respects. Spectroscopically the absorption bands were identical with those of normal oxyhemoglobin and no traces of abnormal substances (methemoglobin, sulphemoglobin) were detected. The decomposition products gave normal crystals and the usual spectra. The increased iron content (90 mg) was proportional to the red cell count, resembling normal blood in this respect also (from 42 to 52 mg with counts ranging from 4,500,000 to 5,000,000) being approximately a proportion of 10 mg to each million corpuscles enumerated per cubic millimeter. The hemoglobin content (193.6 per cent) calculated from the iron content was slightly higher than the reading on the Sahli scale. The highest reading obtained on one occasion was 210 on the Sahli scale. The oxygen combining power of the hemoglobin gave readings for the hemoglobin of from 163.6 to 170.8 per cent.

The carbon dioxide combining power of the plasma showed a slight lowering of the alkali reserve (43.5 volume per cent). The oxygen content of the venous blood from the arm after the patient had clenched his fist several times and then stopped, but was otherwise at complete rest, was 86.12 per cent saturated, or an oxygen unsaturation of 4.38 volumes per cent. This is within Lundsgaard's normal limits for oxygen unsaturation of venous blood in normal persons at rest<sup>14</sup>. It was first thought that some of the cyanosis was caused by the incomplete oxidation of the arterial hemoglobin (although enough oxygen was present for normal physiologic purposes), but the figures do not seem to bear this out.

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<sup>14</sup> Lundsgaard, C. Studies of Oxygen in Venous Blood. I. Technique and Results in Normal Individuals, *J. Biol. Chem.* **33**: 133 (Jan.) 1918.

The relation of the total oxygen combining power of the blood, the color index, the hemoglobin and the blood count is shown in Table 3

The hemoglobin content of the corpuscles in terms of the color index remained constant on the two occasions noted above, using similar methods

To carry 374 c c (the basal rate) of oxygen to the body per minute, it would require 1219 c c of the patient's blood to pass through the heart per minute. This comparatively small amount may account for the lack of hypertrophy of the heart

TABLE 3—LABORATORY DATA OBTAINED IN EXAMINATION OF BLOOD

	June 6, 1922	June 20, 1922
Red cell count	9,240,000	9,640,000
Percentages of "normal"	184.8%	192.8%
Hemoglobin (Van Slyke)	163.6%	170.8%
Oxygen bound by 100 c c blood (saturated)	30.07 c c	31.61 c c
Color index	0.88	0.88

#### SUMMARY

1 A case of polycythemia vera with an unusually high red cell count is reported. Counts at intervals during three years varied from 7,360,000 to 15,940,000

2 A tentative explanation and correlation of some of the features of the abnormal physiology is given. (High basal metabolism, polycythemia, high uric acid, high iron, high minute volume of air breathed, slow vital capacity, nucleated red cells, increased corpuscle resistance, prolonged coagulation time, increased volume of corpuscles, high viscosity, low surface tension.)

3 A normal and significant endogenous source of uric acid from nuclear material from developing erythrocytes is outlined

4 In the three conditions—erythremia, leukemia and pernicious anemia, the basal metabolic rate and the uric acid content of the blood are increased at times. The diversity of the conditions and the common point of the destruction of nuclear material of the blood elements suggests a relationship between the increased basal metabolic rate and the uric acid production

5 The high viscosity of the blood under conditions found in the extremities, and the comparatively low blood pressure suggest a local source of origin for the pain

6 The depth of color is apparently independent, to a certain extent, of the blood count, and appears to depend on the state of the capillaries

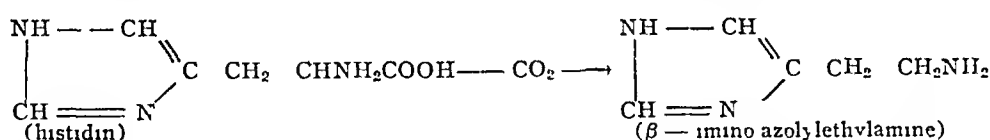
# THE ETIOLOGY OF ACUTE INTESTINAL INTOXICATION IN INFANTS \*

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Acute intestinal intoxication in infants has been generally regarded as due to an infection. The lack of any unanimity of opinion among workers in this field as to the responsible organism, lead us to consider the possibility of the toxemia being due to a chemical toxin, in the production of which various types of organisms might play a more or less important part. Schloss<sup>1</sup> recently reported the finding of a substance of unknown nature in the blood of cases of intestinal intoxication which proved to be toxic to guinea-pigs.

Starling,<sup>2</sup> in 1902, and later Popielski,<sup>3</sup> reported the finding of a toxic substance in extracts of normal intestinal mucous membrane. This toxin, when injected into animals, caused a symptom complex consisting of increased peristalsis, periods of depression and narcosis, vasodilation, and fall of blood pressure. Barger and Dale<sup>4</sup> regarded this substance as identical with the amine base  $\beta$  imino-azolyethylamine (histamine) which they found in extracts of the intestinal mucous membrane of the ox. Mellanby and Twart,<sup>5</sup> in 1912, and more recently, Hanke and Koessler,<sup>6</sup> demonstrated the ease with which histidin, a normal innocuous constituent of the intestine, could be rendered toxic by the replacement of an acid by an alkyl radical, as in the following equation, by the action of certain strains of the colon bacillus



Barger and Dale<sup>7</sup> found that amines were usually rendered less toxic by the change from an acid to an alkyl compound of the group. Ewins and Laidlaw<sup>8</sup> studied the fate of one amine, parahydroxyphenyl-

\* From the Wards and Nutritional Research Laboratories, Hospital for Sick Children, and the Department of Pediatrics, University of Toronto.

\* The animals for this work were provided by the Committee for Experimental Research, University of Toronto.

1 Schloss, O. M. Proc. Soc. Exper. Biol. Med. **18** 101, 1921.

2 Starling, J. Physiol. **28** 335, 1902.

3 Popielski, Arch. f. d. ges. Physiol. **128** 191, 1909.

4 Barger and Dale, J. Physiol. **41** 500, 1911.

5 Mellanby and Twart, J. Physiol. **45** 180, 1912.

6 Hanke and Koessler, J. Biol. Chem. **50** 131, 193, 235, 271, 1922.

7 Barger and Dale, J. Physiol. **41** 19, 1910.

8 Ewins and Laidlaw, J. Physiol. **41** 78, 1910.

ethylamine, in the body by perfusion experiments and found it normally detoxicated by the liver, uterus and heart, which converted it into parahydroxyphenylacetic acid

Mellanby<sup>9</sup> suggested that  $\beta$  imino-azolyethylamine was the cause of diarrhea and vomiting in children. He injected the substance into the intestine of cats and attempted to determine what factors influenced its absorption. Toxemia might arise from the increased absorption of this substance from the intestine.

Rohmer and Levy<sup>10</sup> recently demonstrated an increased permeability of the intestinal wall to both crystalloids and colloids in intestinal intoxication, but considered the increase insufficient to account for the symptoms produced.

Our experiments were made on material obtained from cases of acute intestinal intoxication in infants. Attempts were made to determine the presence and nature of any toxic substance in extracts of the intestinal mucous membrane, which might account for the intoxication. The conditions under which material must be obtained in order that results will not be vitiated by the action of putrefactive organisms, renders it impossible to obtain a large number of cases in a short time.

The beneficial effects of exsanguination transfusion, which was observed clinically in these cases, suggested the advisability of the determination of the toxicity of the blood when injected into animals. Both systemic and portal blood were used for this purpose.

1 *Preparation of the Extract of the Intestinal Mucous Membrane*—The gastro-intestinal tract was removed intact as soon as possible after death, usually within about two hours, and never more than three. It was thoroughly washed with tap water and placed in the refrigerator for about twelve hours. The mucous membrane was then scraped off with a sharp scalpel and ground with sea sand. Dilute hydrochloric acid was then added to this mass to a concentration of 0.1 per cent hydrochloric acid and the whole boiled three minutes. This was cooled, nearly neutralized and filtered through a Buchner funnel. The filtrate was concentrated and filtered through a Berkefeld filter. The filtrate obtained in this way was used for animal inoculation. About 100 c c of extract were obtained from each case. Portions of the filtrate were further treated by Kutscher's method for isolating organic bases. Twenty per cent tannin was added drop by drop until flocculation occurred. Excess was avoided as it rendered the filtrates turbid. The filtrate obtained was pale yellow and water clear. Excess silver nitrate was added in the presence of baryta water, and the resultant precipitate collected and dissolved in hot absolute alcohol. The alcohol was then

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<sup>9</sup> Mellanby. *Quart M J* 9 165, 215 1915

<sup>10</sup> Rohmer and Levy. *Arch d med des enf* 25 65, 1922

removed and the yellowish, slightly viscid, residue was treated with saturated aqueous solution of picric acid. Yellow crystals formed, which were dissolved in dilute hydrochloric acid, and repeatedly shaken with ether to remove picric acid. The ether was removed by evaporation. The crystals were yellow, serrated rhomboids, from 0.5 to 1 cm in length, which melted at from 235 to 244 C., to form red smears. These crystals were obtained in small amounts in four out of five cases in which this process was carried out. The crystals were later boiled for two or three hours in absolute alcohol, as they proved innocuous when injected into animals without this procedure.

#### ANIMAL INOCULATION

1 *Extracts of Intestinal Mucous Membrane*—To ensure success in the animal experiments it proved essential to use only young animals, the older ones proving not susceptible to the doses which were found very toxic, or fatal, in the younger animals.

(a) *Rabbits* Doses of the concentrated extract, up to 15 c c, given per os failed to produce any symptoms other than slight anorexia. Three rabbits, about 1,200 gm in weight, were given from 6 to 10 c c doses of the extract intraperitoneally. Within a short time the respiratory rate increased a little, there was evidence of circulatory failure, varying degrees of narcosis and depression, and a slight increase in the number of intestinal evacuations. One of these rabbits became progressively worse and died on the fifth day. Post-mortem examination showed nothing but slight fatty changes in the liver and in the renal tubules. Two other rabbits were dehydrated previous to giving the extract. The evidences of the toxemia were more marked but both animals recovered. Three other rabbits were given 4 c c doses of regenerated crystals, i. e., crystals obtained from the extract of intestinal mucous membrane which had been boiled for a long time in alcohol which was then removed and the crystals dissolved in saline solution. Four c c would equal about one-tenth of the total yield from an individual case. Two of these rabbits died, following symptoms like those exhibited by the others, only with more marked narcosis. No characteristic changes were seen at the necropsy.

(b) *Kittens* Doses of the extract up to 20 c c when given per os had little or no effect on the animal. Two kittens were given 10 c c doses intraperitoneally. Of these, one collapsed, showed circulatory failure, and died in fifteen minutes, the other showed no symptoms at all. Intraperitoneal administration of from 2 to 6 c c doses of the saline solution of regenerated crystals was followed at once by a typical train of symptoms, periods of depression and narcosis, anorexia, increased frequency of intestinal evacuation and finally convulsions and



death in from two to four days. The necropsies presented nothing distinctive, the slight fatty changes in the liver and kidney, and some alveolar hemorrhage being the only abnormal findings.

(c) *Pigs* Guinea-pigs proved not susceptible to this toxin. Young pigs of between 300 and 400 gm weight were used, but failed to show anything more than a slight anorexia, even with intraperitoneal injections of the extract.

(d) *White Mice* Two c c doses of the concentrated extract given intraperitoneally to four mice, proved fatal to three. Almost immediately after the injection, general convulsions started, these alternated with periods of narcosis until death, in the fatal cases, and recovery in the other.

Two c c doses of saline solutions of unregenerated crystals (not subjected to boiling with alcohol) given intraperitoneally failed to produce any symptoms at all. Similar doses of the regenerated crystals caused death in all of our animals that were inoculated.

2 *Stool Extracts*—Fresh stools were mixed with enough saline to make the total volume 100 c c, boiled three minutes, filtered with suction, and then through a Berkefeld filter. This filtrate was used for injection into animals.

Rabbits fed up to 25 c c of this extract exhibited no toxic symptoms. Doses of from 5 to 10 c c injected intraperitoneally into pigs produced only temporary evidences of a mild toxemia.

3 *Blood Injections*—Five pigs were given 5 c c doses of whole blood from patients acutely ill with acute intestinal intoxication. All showed slight drowsiness and anorexia but not much more marked than is sometimes noted after the administration of normal whole blood.

Two pigs were given 15 c c doses of portal blood, obtained at necropsy from fatal human cases. Both responded almost immediately by severe convulsive twitchings, succeeded by drowsiness and anorexia and increase in the number of stools. These symptoms lasted twenty-four hours. Both animals made a complete recovery.

#### SUMMARY

1 Extracts of intestinal mucous membrane from cases of acute intestinal intoxication in children contain a toxic substance, which, when injected into animals, produce a definite symptom complex, consisting of depression and narcosis, anorexia, circulatory failure, increase in the number of intestinal evacuations, and in some cases convulsions and death.

2 Younger animals were much more susceptible to this toxic substance than older ones.

3 The toxin is not destroyed by boiling and passes through a bacteria tight filter

4 Crystals resembling those of the dipicrate of  $\beta$  imino-azolyethylamine were obtained by appropriate means, from the extracts of intestinal mucous membrane

5 These crystals proved innocuous in animals until their basic character was restored by prolonged boiling with alcohol, when they became highly potent

6 Previous dehydration of an animal rendered it more susceptible to the toxin

7 Boiled aqueous extracts of fresh stools proved nontoxic when injected into animals

8 Systemic blood from cases of acute intestinal intoxication was slightly toxic when injected into animals

9 Portal blood from patients was very toxic

10 No distinctive pathologic findings were seen in any of the fatal cases

## BOOK REVIEW

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THE PRACTICE OF MEDICINE By A. A. SILVENS, A.M., M.D., Professor of Applied Therapeutics in the University of Pennsylvania. Cloth. Price, \$8.50. Pp. 1106, with 35 illustrations. Philadelphia: W. B. Saunders Company, 1922.

The usual single volume standard practice of medicine must necessarily briefly define and describe and give the treatment of a very large number of diseases and conditions. It is intermediary between the quiz compends and the larger systems of medicine, and certainly has great practical value for the student and busy practitioner. This book follows the usual plan and is comprehensive, concise and up to date. The bibliography is incomplete and poorly given, but in a work of this kind a bibliography is not essential or even necessary. Large numbers of prescriptions are given, and one questions the advisability of this, as the exact amounts and proportions of the ingredients might be thought to be indicated in each and every case. Perhaps it is impossible for one who has written largely on the subject of materia medica to refrain from including such formulas. The sections on treatment may be somewhat bewildering to one seeking definite information, because of the large number of drugs "said to be useful."

## FURTHER OBSERVATIONS ON THE ROENTGEN-RAY TREATMENT OF TOXIC GOITER<sup>1</sup>

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  - B Toxic Adenoma (Table 2, Fig 5)
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- VI DISCUSSION OF RESULTS
  - A Reasons for believing that roentgen-ray has an action in toxic goiter
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  - C Proper use to make of roentgen-ray in toxic goiter Relation to other sorts of therapy Results to be expected, limitations
- VII CONCLUSIONS

### I INTRODUCTION

A study of toxic goiter with special reference to the results obtained with various forms of treatment, as shown by clinical and metabolism findings, was begun in this clinic in 1914<sup>1</sup> The forms of treatment that have been studied to date are the surgical procedures of ligation of vessels and partial thyroidectomy, and the exposure of the thyroid gland to the roentgen ray In this work there has been close cooperation between internist, surgeon and radiologist Our aim has been to form an unbiased opinion of the relative merits and limitations of the therapeutic measures under investigation

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\* From the Medical Service and Roentgenologic Department of the Massachusetts General Hospital, aided in part by a gift from Dr William Norton Bullard

1 Means, J H Basal Metabolism and Body Surface, J Biol Chem 21 263, 1915

Several reports on this work have already appeared. The earlier metabolism data were published by Aub and Means in 1917,<sup>2</sup> and again in 1919,<sup>3</sup> and by Means.<sup>4</sup> In 1919 Holmes and Merrill discussed the method of giving roentgen-ray treatment, the dangers incident to its use, and the selection of cases.<sup>5</sup> A further report from the roentgenologist's point of view was made by Holmes in 1921.<sup>6</sup>

Our object now is to report in full the clinical and metabolism findings in certain cases treated by the roentgen ray during the last three years, and the end results in cases studied earlier, and to discuss the matter of the roentgen-ray treatment, its value and its limitations as we see them in the light of our experience up to the present time.

Our discussion will be based on forty-four new cases of exophthalmic goiter and fourteen cases of toxic adenoma, as well as on nine cases reported earlier. This group does not include all patients that have been treated by the roentgen ray, but it does include those in which we feel that we have sufficient data to draw an accurate conclusion regarding the action of the roentgen ray. For example, cases with incomplete metabolism data and those in which surgical operations were performed coincident with the roentgen-ray treatment have not been included. The cases treated by surgery alone or by surgery and the roentgen ray at the same time will be discussed by our surgical colleagues in separate papers. The present discussion of the results of roentgen-ray therapy should be read in conjunction with those on surgery when they appear.

## II HISTORICAL

The discovery of the roentgen ray was announced by Rontgen in December, 1895. The significance of this discovery for medicine was grasped almost at once, and although at first attention was centered chiefly on its use for diagnosis, we find within the year suggestions that the rays had a therapeutic application as well. Lortet and Genoud,<sup>7</sup>

2 Means, J. H., and Aub, J. C. Study of Exophthalmic Goiter from the Point of View of the Basal Metabolism, *J. A. M. A.* **69** 33 (July 7) 1917.

3 Means, J. H., and Aub, J. C. Basal Metabolism in Exophthalmic Goiter, *Arch. Int. Med.* **24** 645 (Nov.) 1919.

4 Means, J. H. Hyperthyroidism. Toxic Goiter, *M. Clinics N. America* **3** 1077, 1920.

5 Holmes, G. W., and Merrill, A. S. Treatment of Thyrotoxicosis by Means of the Roentgen Ray, *J. A. M. A.* **73** 1693 (Nov. 29) 1919.

6 Holmes, G. W. Some Observations on the Treatment of Hyperthyroidism with Roentgen-Rays, *Am. J. Roentgenol.* **8** 730, 1921.

7 Lortet, L., and Genoud. Tuberculose expérimentale atténuée par la radiation Röntgen, *Gaz. d'hôp. de Par.* **69** 787, 1896.

for example, believed that they could attenuate experimental tuberculosis infections, and Thomson<sup>8</sup> and others noted the burning effect of the rays on human skin. In a paper published by Bleyer<sup>9</sup> only two months after the discovery of the roentgen ray, we find an interesting prophecy that because of their resemblance to light the roentgen rays would prove to have their place in therapeutics. Five months afterward Despeignes<sup>10</sup> reported his attempts to relieve cancer of the stomach by the rays and, in July, 1897, Bergonie and Mongour<sup>11</sup> reported their results in cases of pulmonary tuberculosis. Bergonie,<sup>12</sup> in January, 1897, remarking on Thomson's discovery of the roentgen-ray burn, predicted that further study would prove the therapeutic value of the rays. The first successful therapy was probably that of Freund,<sup>13</sup> who in March, 1897, reported his observations on a case of hairy pigmented naevus which he had completely relieved by the rays. He was led to try the roentgen ray in this case because of the observation that the rays apparently could cause alopecia.

We have been unable to determine beyond doubt who was the first to use the roentgen rays in the treatment of goiter. The paper of Beck,<sup>14</sup> who in 1900 reported some observations on cases of nontoxic goiter, is the earliest we have found. In 1902, F. H. Williams<sup>15</sup> reports that he had some encouraging results in the treatment of exophthalmic goiter by the rays. Pusey<sup>16</sup> also was among the pioneers in the irradiation of toxic goiter. It is interesting to note that the roentgen rays were used in goiter earlier than in leukemia, the first observations in the latter disease having been made by Senn in 1903.<sup>17</sup>

8 Thomson, E. The Cause of Burns from Roentgen-Rays, Boston M & S J **135** 610, 1896

9 Bleyer, J. M. Crook's X and Other Rays, a Problem Yet to be Solved in Therapeutics, New York M J **63** 245, 1896

10 Despeignes, V. Nouvelle observation de cancer traite par les rayons de Roentgen, Lyon med **82** 428, 1896, **83** 550, 1896

11 Bergonie, J., and Mongour, C. Les rayons Rontgen ont-ils une action sur la tuberculose pulmonaire de l'homme, Bull de l'Acad d med Par **38** 66, 1897

12 Bergonie, J. Les radiations de Roentgen et leur emploi en medicine, J de med de Bordeaux, **27** 37, 1897

13 Freund, L. Ein mit Rontgen-Strahlen behandelter Fall von Naevus pigmentosus piliform, Wien med Wchnschr **47** 428, 1897

14 Beck, C. Beitrag zur Diagnostik und Therapie der Struma, Fortschr a d Geb d Rontgenstrahlen **4** 122, 1900

15 Williams, F. H. Roentgen Rays in Medicine and Surgery, Ed 2, New York, Macmillan Co, 1902

16 Pusey, W. A., and Caldwell, E. W. Practical Application of Rontgen Rays in Medicine and Surgery, Philadelphia, W. B. Saunders Co, 1903

17 Senn, N. Case of Spinomedullary Leukemia Successfully Treated by Use of the Roentgen Ray, Med Rec **64** 281, 1903

In 1905, several papers appeared, among others those by Stegmann<sup>18</sup> and by Gorl<sup>19</sup>. The latter makes the definite statement that the roentgen ray has a definite action on the thyroid, but adds that further study will be needed to show in what types of goiter it should be used. In the same year Abbe<sup>20</sup> reported a case of exophthalmic goiter in which radium had apparently been of value.

In 1907, C. H. Mayo<sup>21</sup> made the following statement: "We also make use of the roentgen ray. From its known action on the lymphatics and the glands it exerts a favorable effect on the overactivity of the thyroid in exophthalmic goiter, and in some cases seemingly develops something of a capsule and partially changes the character of the tumor. While its effect may not be permanent, it is a valuable adjunct in preparing advanced cases for surgical procedure." In the same year Freund<sup>22</sup> concluded that "roentgentherapy fulfills the causal indication in exophthalmic goiter in that it causes the morbid thyroid to dwindle. It works favorably on the body weight and on the nervous symptoms, and can diminish other symptoms such as palpitation, goiter and exophthalmos. Soft vascular goiters give the best prognosis, the symptoms clearing the more quickly the more recent they are." (Translation ours)

Pfahler,<sup>23</sup> who was among the early workers in this field and also has kept up a consistent interest and study to the present time, was able in 1908 to collect fifty-one cases from the literature, forty-two of which showed good results after roentgen-ray treatment. His conclusions at that time were: "1. Decided improvement may be expected in about 75 per cent of the cases. 2. This improvement consists of an increase in weight and strength and gradual disappearance of Basedow symptoms. 3. Some improvement should be noted in a month and after from six to twelve treatments. 4. When the treatment is properly given there appears to be no danger, and I can see no objection to recommending the trial of a month in all cases."

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18 Stegmann, R. Die Behandlung der Struma mit Rontgenstrahlen. *Munchen med Wchnschr* 52 1247, 1905.

19 Gorl, L. Ein neues Feld für die Radiotherapie (Strumenbehandlung), *Munchen med Wchnschr* 52 944, 1905.

20 Abbe, R. Exophthalmic Goiter Reduced by Radium, *Arch Roent Ray* 9 215, 1905.

21 Mayo, C. H. Goiter with Preliminary Report of 300 Operations on the Thyroid, *J A M A* 58 273 (Feb 8) 1907.

22 Freund, R. Die Rontgenbehandlung der Basedowschen Krankheit, *Munchen med Wchnschr* 54 830, 1907.

23 Pfahler, G. E. Summary of the Results Obtained by the Roentgen-Ray Treatment of Exophthalmic Goiter, *New York M J* 88 781, 1908.

In 1916 Pfahler and Zulick<sup>24</sup> made a complete survey of the literature to that date. They draw conclusions similar to those of Pfahler eight years before. Among other things they say: "We believe that the trial of treatment (roentgen ray) for one series with an interval of waiting of one month is justifiable in all cases, for if operation is decided on nothing is lost and many operations in this way can be avoided." They also point out that the treatment should be directed toward both thyroid and thymus glands, and they warn against the production of myxedema by too long treatment.

Of the more recent papers we should like to call attention to those of Allison, Beard and McKinley,<sup>25</sup> Fischer,<sup>26</sup> Crile<sup>27</sup> and Schlecht.<sup>28</sup> The first two papers give reports of favorable results from the use of the roentgen ray. Crile, on the other hand, concluded that it accomplished nothing more than rest alone and, therefore, he could see no reason for making use of it in the management of hyperthyroidism.

There is always the danger in the evaluation of therapeutic achievements of a bias on the part of the observer in favor of his own pet method of treatment. The truth in regard to the best treatment for exophthalmic goiter probably lies somewhere between the views of enthusiastic surgeon and enthusiastic radiologist. We have made an honest attempt to avoid such a bias in this paper, and later on our thyroid committee (which is described below) will, as a whole, make a report which, from the composition of the committee, is bound to be fairly free from bias. The conclusions of Schlecht seem to us to be of this sort. They are not unlike those that we have drawn on the basis of our own experience, and are as follows:

A cure of exophthalmic goiter in the sense of a complete restoration of the normal condition is not to be aimed at by roentgenotherapy, but nevertheless we are in a position to expect extensive improvement. Unadapted for such management are only the severest cases, in those especially, in which there already exists a grave cardiac insufficiency. In other respects we stand in the position with all cases of exophthalmic goiter, first of all to try a course of interval therapy in which the roentgen-ray procedure plays a prominent rôle, but without the neglect of the other usual methods of treating the disease. Material improvement of the general condition, subsidence of the subjective nervous symptoms, restoration of the capacity for work, will often be achieved by roentgenotherapy.

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24 Pfahler, G. E., and Zulick, J. D. The Treatment of Exophthalmic Goiter by Means of the Roentgen Rays, *Am J Roentgenol* **3** 63, 1916.

25 Allison, R. G., Beard, A. H., and McKinley, G. A. Roentgen-Ray Treatment of Toxic Goiter, *Am J Roentgenol* **8** 634, 1921.

26 Fischer, J. F. The Roentgen Treatment of Morbus Basedowii, *Acta Radiol* **1** 179, 1921.

27 Crile, G. W. Surgery versus Roentgen Ray in the Treatment of Hyperthyroidism, *J A M A* **77** 1324 (Oct 22) 1921.

28 Schlecht, H. Die Röntgentiefentherapie in der inneren Medizin. *München med Wchnschr* **67** 800 1920.



Among other things, objectively one sometimes sees a decrease in the eye signs, without, however, their entire disappearance. Only in rare cases will the struma materially diminish (Translation ours)

To the literature of the calorimetry of thyroid disease we can refer but briefly. The elevated metabolism in hyperthyroidism was discovered by Magnus-Levy<sup>29</sup> in 1895, and during the next twenty years a certain amount of research was done, but it was not until after the publication of the surface area formula of the Du Boises<sup>30</sup> in 1916 that the calorimetry of thyroid cases became a common clinical procedure. Since 1916, but more especially during the last three years, an extensive literature on the subject has appeared. The significance of basal metabolism as a functional test of the thyroid has been discussed sufficiently in other papers from this clinic.<sup>31</sup>

### III METHODS

*Thyroid Clinic*—All patients with thyroid disease coming to the Massachusetts General Hospital are referred to a special thyroid clinic, where they are seen by members of the medical, surgical and roentgen-ray staff in consultation. A program for the treatment of each case is mapped out, and the period of treatment and study begins. An attempt is made with all new cases of toxic goiter to start with a period in the hospital ward. This is not always possible. Special records are kept of the clinical condition and progress of each patient, and frequent observations of the basal metabolism are made. The members of the staff holding these thyroid clinics constitute a committee for the study of thyroid disease. As pointed out earlier, this report is merely one phase of the work of this group. It is published now because it seems sufficiently advanced to warrant certain definite conclusions. These conclusions have been concurred in by the surgical members. It is proposed, however, to publish later a combined opinion of the committee as a whole on the treatment of toxic goiter in all its aspects.

*Calorimetry*—The calorimetry is carried out with apparatus of the Benedict type, the technic used has been sufficiently discussed in

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<sup>29</sup> Magnus-Levy, A. Gaswechsel bei Thyroidea, Berl klin Wchnschr **32** 650, 1895

<sup>30</sup> Du Bois, D., and Du Bois, E. F. Formula to Estimate Approximate Surface Area, Arch Int Med **17** 863 (June) 1916

<sup>31</sup> Means, J. H. Studies of the Basal Metabolism in Disease and Their Importance in Clinical Medicine, Boston M & S J **174** 864, 1916, Determination of the Basal Metabolism as a Method of Diagnosis and a Guide to Treatment, J A M A **77** 347 (July 30) 1921. Means, J. H., and Burgess, H. W. Basal Metabolism in Nontoxic Goiter and in Borderline Thyroid Cases, Arch Int Med **30** 507 (Oct) 1922

earlier papers<sup>32</sup> The normal standards of the Sage Institute are used for comparison with the patients' metabolism<sup>33</sup>

*Method of Treatment*—In treating our cases of toxic goiter with the roentgen ray, we have proceeded on the principle that the effect of the radiation will be greater (1) the larger the amount of radiation absorbed, and (2) the more active and less stable the cells composing the gland are at the time of exposure In developing our technic we have kept these principles constantly in mind To obtain the largest possible dose without injury to the skin, we have used rays of relatively short wave length, a long target skin distance and three or more portals of entry In the selection of cases, only those have been chosen for treatment which showed definite signs of glandular hyper-activity (both clinically and in the metabolism)

The formula for dosage has been varied somewhat in individual cases, and has been changed from time to time in attempts to increase the effect At no time has the accuracy in measuring the dose been all that could be desired Some of our failures at least may be due to insufficient dosage, as we have been especially careful not to produce a permanent injury to the skin With a probable error in dosage of 25 per cent, if we continually avoid an overdose, the resulting dose may be sometimes as small as 50 per cent below that intended The skin of patients suffering from hyperthyroidism is more sensitive than the skin of normal persons We have found a reduction of at least 25 per cent necessary if reddening and tanning are to be avoided, and it has been our experience that even the slightest tanning may be followed by permanent injury to the skin, such as atrophy and telangiectasia Any tanning or reddening, therefore, must be avoided in all but severe cases in old women and in men

The effect of the radiation is undoubtedly increased by repeating exposures, and if the exposures are given oftener than once in three weeks the effect is cumulative

Taking advantage of this fact, we have tried following the original dose by fractional doses sufficient to keep the tissues saturated, but in the small number of cases tried, we have not observed any improvement over the usual method of exposure Whatever the method employed is, it is not advisable to continue the treatment beyond five months unless very definite benefit has been obtained

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32 Means, J H Studies of the Basal Metabolism in Obesity and Pituitary Disease, J M Research **32** 121, 1915 Means, J H, and Woodwell M N Remarks on Standards for Normal Basal Metabolism, Arch Int Med **27** 608 (May) 1921

33 Aub, J C, and DuBois, E F The Basal Metabolism of Old Men, Arch Int Med **19** 823 (June) 1917

In the majority of cases reported in this paper, the exposures have been made at 8 inch target skin distance, using a Coolidge tube energized with a rectified current of a voltage capable of breaking an 8 inch air gap between blunt points. The rays have been filtered through 4 mm of aluminum and one thickness of sole leather. The exposure time and the number of milliamperes passing through the tube are varied somewhat, but their product has been kept fairly constant, from 35 to 40 milliamperere minutes being the usual exposure.

For the past year, we have not given any treatment of less than 10 inch target skin distance, and have given several at from 12 to 16 inch distances. This increase of distance, of course, requires a corresponding increase in time of exposure. Three areas are exposed, one on each side of the neck over the thyroid region, and one over the upper part of the sternum in the region of the thymus. The size of the areas exposed has varied considerably but has usually been a square with a diameter of about 3 inches.

Recent studies by Friedrich,<sup>34</sup> Duane<sup>35</sup> and others have shown that increase in the size of the area exposed increases to a considerable extent the effect of the radiation in the deep tissues, because of the amount of secondary radiation produced. Ignorance of this fact, and failure to keep the size of the radiated fields uniform, may have resulted in variation of doses. At present, we are using a measured field.

As already indicated, the interval between treatment has usually been three weeks. Any shortening of this period is likely to produce tanning and should be avoided, except in selected cases.

At each treatment, a prescription indicating the various factors from which the dose is computed is written and signed by the physician in charge of the treatment. The actual giving of the treatment is done by graduate nurses especially trained in roentgen-ray technic. In this way a double check is kept on the dosage. Wooden tables are used to avoid danger from electric shock, and all parts of the patient's body are protected, except the part being treated, from scattered rays by ray proof cloth.

#### IV PRESENTATION OF DATA

As we have indicated earlier, this study is based on two groups of cases. One group comprises those cases treated within the last three years, the other group consists of cases treated before the war. The

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<sup>34</sup> Friedrich, W, and Kroenig, B (Translated by Schmitz) *Radiation Therapy*. Ed 2 New York, Rebman Co., 1922

<sup>35</sup> Duane, W. Personal communication

former will serve for an analysis of the early effects of roentgen-ray therapy, the latter for a study of end results

The data on both groups is given in Tables 1, 2 and 3, the data of the recent group being given in Tables 1 and 2<sup>36</sup>

To visualize the progress of the disease, charts are rather more easy of interpretation than tables. We cannot take the space to give the individual charts of all our patients. A study of certain composite charts, however, may serve a useful purpose. We will present these first and then discuss certain individual cases to illustrate special points.

**THE RECENT SERIES *Exophthalmic Goiter***—Of our fifty-eight new cases, forty-four were cases of exophthalmic goiter and fourteen were cases of adenoma with hyperthyroidism (toxic adenoma). It will be best to examine these separately.

Of the forty-four exophthalmic goiter cases, sixteen showed little or no improvement, eight of these came to operation later and were apparently cured. Of the twenty-eight cases in which there was improvement, twelve were apparently cured and sixteen were improved but were not rendered entirely free from hyperthyroidism. No cases seemed to be made worse by the treatment. Two patients who were improved but not cured were later subjected to operation. One of these patients died following operation. So far as we know she is the only patient out of the fifty-eight under discussion who has died.

An impression of the usual effect of the roentgen ray in those cases of exophthalmic goiter in which it has any demonstrable effect (64 per cent of the cases in the present series) can be obtained from a study of composite charts. In Figure 1 we have shown the composite metabolism, pulse and weight curves of the twenty-eight patients who improved. It will be noted that there is a rapid fall in pulse (from 115 to 89) and basal metabolism (from +55 to +21 per cent) and a corresponding gain in weight (9 per cent) in the first four months of treatment, during which time the patients received, on the average five treatments. No further significant drop in pulse or metabolism curves occurred in the next six months, in spite of more treatment. In the second year there was a slight drop.

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<sup>36</sup> In this paper, as in the previous papers by Means and Aub,<sup>3, 4</sup> the cases are referred to by their laboratory numbers. In the paper by Holmes,<sup>6</sup> however, they are referred to by the roentgenologic department numbers. So that the reader may identify the cases that appeared in Holmes' paper and in this paper the following key is given:

Laboratory No	Roentgenologic No	Laboratory No	Roentgenologic No
224	3646	819	3993
566	3763	621	3611
734	3923	575	3869
623	3933	348	3740

TABLE 1.—DATA ON EXOPHTHALMIC GOITER CASES

Lab No., Age, Duration of Disease	Date	Weight, kg	Pulse	Basal Metabo- lism, %	Acti- vity	Röntgen Ray Treatments Dates	Goiter	Exoph- thalmos	Tremor	Cardiac Condition	Remarks
No 224 Mrs M J Age, 41 Duration, 1 yrs	3/29/18	52	125	+85	1	Apr 29, June 10, July 21, Aug 15, Oct 18 Dec 17, 1918, Jan 20, Apr 21, May 12, June 3, 1919	+++	++	++	Compensated mitral disease	Moderately severe Also chronic cardiac
	4/5/18	49	112	+78	1						
	4/20/18	48	132	+80	1						
	1/27/19	63	88	+44	2						
	2/3/20	61	76	-2	2						Writes that she is well
	12/6/20	67	72	+2	2						
	3/20/22				3						
No 316 Mrs F D Age, 43 Duration, 2 yrs	8/21/19	59	76	+51	1	Sept 8, Sept 29, Oct 20, Nov 10, 1919 Dec 1, Dec 22, 1919 Mar 1, Apr 26, 1920 June 28, 1920 Sept 15, Nov 13, 1920 Jan 12, Feb 16, 1921	+	+++	++	Slightly +	Moderately severe Also cardiac
	8/29/19	57	94	+51	1						
	12/1/19	58.5	76	+28	3			++	+		Subjectively much improved
	3/1/20	62	80	+33	3			++	0		
	6/28/20	63	88	+25	3			+	0		Continued improvement subjectively Chiefly cardiacrenal now
	9/15/20	60.5	84	+37	3						
	12/20/20	63.5	76	+20	3						
	12/9/21	64.5	74	+24	3						
No 319 Miss E C Age, 38 Duration, 2 mos	8/27/19	54	114	+56	3	Oct 4, Oct 25, Nov 15, 1919 Dec 27, Feb 21, Apr 3, 1920 Apr 21, 1920 Jan 14, 1922 Feb 4, 22, Feb 24, 1922	Rt +, Left 0 Same	Rt +, +, +, Left +, Rt +, +, Left +, R +, +, L + Same Same Same	++	Normal	Recent and mild case
	12/6/19	55	112	+39	3				+		Looks and feels much better
	4/24/20	53	92	+20	3				0		Clinically well
	7/7/20	53.5	92	+16	3						Remains clinically well
	10/2/20	61.5	80	+9	3		0				Started roentgen ray again Feels well
	5/14/21	65.5	98	+23	3		0		+		Improving objectively Feels well
	12/17/21	62	102	+26	3		0		+		Clinically well
	2/4/22	62	87	+19	3						
	2/27/22	62.5	51	+5	3						Mild stationary case
No 328 Miss T G Age, 25 Duration, 2 years	9/15/19	52.5	110	+27	2	8 previous treatments Sept 22, Oct 20, 1919 Nov 24, 1919 Mar 1, June 1, 1920 June 21, July 14, Aug 4, 1920	++	+	+	Normal	16 roentgen rayings with no improve- ment On October 18, sup arteries ligated
	11/24/19	52.5	116	+39	2						
	11/26/19	52.5	100	+39	2						
	11/28/19	52.5	104	+35	2						
	12/1/19	52.5	104	+34	2						
	12/3/19	52.5	106	+34	2						
	12/12/19	52.5	114	+21	2						
	12/19/19	52.5	112	+20	2						
	3/1/20	52	110	+26	2						
	6/20/20	50	104	+31	2						
	11/1/20	48	120	+21	1						
	12/14/20	45.5	120	+36	2		++	+	+		
	12/23/20	45.5	116	+28	2						
	1/6/21	45.5	114	+35	2						
	3/11/21	45.5	68	-9	1						
	3/22/21	46.5	70	-4	1						
	11/1/21	53	98	+7	3		0	+	0	Normal	On February 19, subtotal thyroidectomy Clinically well
No 329 Mrs M R Age, 31 Duration 16 mos	9/15/19	52	120	+73	3	8 previous treatments Sept 29, Oct 27, Nov 17, 1919	++	++	+	Normal	Moderately severe No improvement after 8 roentgen rayings
	3/3/20	45.5	128	+66	3						
	3/10/20	44	120	+54	1						No improvement after 11 roentgen ray- ings
	3/17/20	44	106	+41	1						
	3/23/20	43	112	+54	1						

	4/ 3/20 6/ 7/20 7/ 7/20 10/ 4/20 2/26/21 5/ 7/21 11/ 5/21	41 5 47 42 5 50 5 57 5 60 5 64 5	116 108 96 92 98 92 80	+45 +45 +15 +21 +21 +24 +14	1 1 1 3 3 3 3			0 +	+	0 +		On March 26, sup arteries ligated On June 16, subtotal thyroidectomy Clinically much improved Clinically well
No 367 Miss G G Age 24 Duration, 3 years	10/18/19 10/23/19 10/24/19 10/25/19 11/17/19 12/ 8/19 12/29/19 3/29/20 9/20/20 10/25/21	56 56 56 57 5 57 58 55 5 55 5 50 5 47 5	124 96 98 98 120 112 80 88 80 74	+33 +16 +18 +17 +38 +27 +13 + 7 + 9 +10	1 1 1 2 3 3 3 3 3 3	Oct 23, 1919  Nov 17, 1919 Dec 8, 1919 Dec 29, 1919 Mar 29, 1920	++  + +	++  + 0	+	++	Slightly +	Mild, but symptoms increasing  Much improved Clinically well
No 371 Miss A B Age 23 Duration, 3 years	10/21/19 11/13/19 2/ 6/20 4/ 7/20 9/27/20 1/15/21 3/19/21 11/16/21 1/18/22	66 66 5 62 5 56 60 64 66 66 5 66 5 72	124 120 118 120 112 116 94 88 89 101	+60 +70 +63 +48 +51 +10 +24 +19 +16 +13	2 2 2 1 2 2 3 3 3 3	Oct 21, 1919 Nov 13, Dec 15, 1919, Jan 16, 1920 Feb 6 1920 Apr 12 May 11, June 1, 1920 June 24, 1920	+++ +++ +	++ +	+	+	Not + Syst mur	Moderately severe Stationary Slight improvement after 4 \x ravings On March 6, rt sup artery ligated On March 20, left sup artery ligated Objectively better, subjectively not Much improved Married June 4 Clinically well Six months pregnant
No 376 Mrs R N Age 27 Duration, 1 year	10/22/19 1/ 5/20 3/24/20 6/13/20 11/11/20 12/ 8/21	43 45 5 46 48 49 5 51 5	122 114 96 80 76 75	+45 +51 +23 + 3 + 7 — 2	3 3 3 3 3 3	Oct 22, Nov 12, Dec 1, 1919 Jan 5, Jan 26, Feb 16, 1920 Mar 24, Apr 14, May 24, 1920	+	+	+	Slightest +	Normal	Moderately severe Stationary Very much improved Clinically well Clinically well
No 383 Mrs B S Age 43 Duration, 3 years	10/29/19 1/ 9/20 6/25/20 11/ 4/20 2/17/21 5/13/21 10/ 4/21 3/ 7/22 4/ 3/22	48 50 5 57 5 55 55 5 57 57 5 56 5 57	98 84 86 92 97 88 93 104 90	+21 +21 +12 +11 +26 + 5 +16 +33 +10	1 2 2 2 2 2 2 2 2	Oct 29, Nov 20 Dec 11, 1919 Feb 10, Mar 2, Mar 23, 1920  Feb 18, Mar 11, Apr 1, Apr 22, 1921	+	+	++ +		Slight myo cardial weakness	Mild chronic case Golter heart  Improved  Not so well On March 16, subtotal thyroidectomy
No 386 Mrs R G Age 33 Duration, 1 year	10/31/19 12/10/19 12/24/19 1/ 5/20 4/15/20 7/24/20 6/ 9/20 6/28/20 10/ 0/20 7/13/21 9/16/21	51 47 40 45 5 46 5 44 5 48 47 51 5 50 5 55	96 108 90 90 98 86 104 100 78 78 65	+51 +91 +59 +79 +69 +53 +12 +79 +23 +28 +21	2 2 1 1 1 1 2 1 3 3 3	Oct 31, Nov 22, Dec 15, 1919  Jan 5, 1920	++  +	++  +	+		Enlarged syst mur	Moderately severe Symptoms increasing Worse Improved slightly  On April 16 sup arteries ligated  On June 11, subtotal thyroidectomy Much improved Much improved

TABLE 1—DATA ON EXOPHTHALMIC GOITER CASES—(Continued)

Lab No., Age, Duration of Disease	Date	Weight, Kg	Pulse	Basal Metabo- lism, %	Activ- ity	Röntgen Ray Treatments Dates	Goiter	Exoph- thalmos	Tremor	Cardiac Condition	Remarks
No 389 Mrs A H Age, 42 Duration, 2 yrs	11/ 1/19	60	120	+76	1	Nov 6, 1919  Nov 24, 1919	++	-	+++	Not + syst, mur	Moderately severe
	11/ 8/19	57.5	92	+58	1						
	11/22/19	56.5	100	+75	1						
	11/29/19	56.5	96	+69	1	Dec 15, 1919 Jan 1, 1920	++	+	+++		No improvement
	12/11/19	55.5	96	+64	1						On January 9, sup arteries ligated
	12/24/19	54.5	96	+63	1						On February 9, subtotal thyroidectomy
	1/ 7/20	54.5	110	+64	1		0	0	0		Clinically well
	1/20/20	52.5	102	+55	1		0	0	+		Slight return nervousness Getting obese
	2/ 2/20	52.5	100	+39	1						
	2/17/20	52	95	+18	1	Nov 28, Dec 19, 1919, Jan 16 1920 Feb 9, Mar 1, Mar 22, Apr 12, May 4, 1920 Oct 25, 1920	0	+	+	Moderate + syst mur	Mild stationary ease
	2/28/20	52	74	+ 6	3		0	Less	Less		Subjectively better
	1/22/21	72	84	+ 4	3		0	Less	0		Subjectively much improved
No 405 Mrs J J P Age, 62 Duration, 3 years	11/ 7/19	51.5	82	+48	2						More improvement
	2/ 9/20	54.5	100	+46	2						
	10/14/20	55	150	+44	2						
	4/10/22	51.5	95	+29	2	Nov 10, Dec 2, 1919 Dec 23, 1919 Jan 14 Feb 4, Feb 26, 19.0 Mar 19, July 12, 1920 Oct 22, Nov 13, 1920	+	+	+++		Recent, moderately severe ease
	11/10/19	63	120	+61	2		+	+	+++		Subjectively slightly better
	12/22/19	63	120	+75	2		+	+	+++		Subjectively further improvement
	1/14/20	64.5	106	+60	2		Less	Less	+		Better
	3/19/20	78.5	88	+25	2						Not so well
	8/19/20	74	108	+42	2						Better, but still slightly thyrotoxic
	10/21/20	77.5	78	+20	3		0	0	0		Clinically well
	1/15/21	77	87	+46	3		0	0	0		
	5/ 1/21	77.5	87	+46	3						
No 431 Miss P R Age, 29 Duration, 1 year	4/29/22	79.5	74	+13	3	Nov 29, Dec 20, 1919, Jan 10, 1920 Jan 31, Feb. 21, 1920	Rt +	+	++	Not + syst mur	Mild and recent
	11/29/19	50	105	+29	3						
	1/31/20	50	98	+26	3						No improvement, 5 roentgen ray-rings
	3/23/20	46	112	+48	1						On March 29, subtotal thyroidectomy
	3/27/20	44.5	88	+34	1		0		0		Much improved
	4/ 9/20	44.5	80	+ 1	1		0		0		Clinically well
	4/ 9/20	44.5	84	+ 0	2						
	10/23/20	55.5	84	+ 0	3						
	11/12/21	58.5	65	+ 3	3						Mild case
	1/14/20	52.5	90	+55	1	Jan 16, 1920 Feb 9, 1920 March 1, March 22, 1920	+	+	+	Not + syst mur	Much improved
	2/ 7/20	49.5	64	+18	1						Myxedema developed, started on thyroid
	2/11/20	49.5	56	+16	1						Better, thyroid stopped
No 485 Mrs J L Age, 29 Duration, 1 year	4/29/20	63	52	-11	3					Same	Myxedema again, started on thyroid
	5/14/20	63.5	48	+ 1	1						
	5/14/20	63.5	48	-11	1						Thyroid stopped Normal appearance
	5/20/20	64.5	48	-11	1						
	6/19/20	64.5	52	+ 3	2						
	6/19/20	63.5	52	+10	2						
	7/28/20	63.5	52	+13	3		0	0	0		Clinically well
	9/28/20	62	52	+11	3						
	11/29/20	62	54	+21	3		0	0	0		Clinically well Four months pregnant
	5/ 5/21	62.5	60	+21	3						
	12/ 8/21	60.5	56	+11	3						

No 499 Mrs N B Age 49 D, 18 mos	1/23/20 4/20/20 4/28/20	52.5 53.5 51.5	132 128 124	+53 +46 +39	2 2 2	Jan 23, Feb 16, Mar 8, Mar 29, 1920 Apr 20, 1920	+	+	+	++	Normal	Moderately severe, getting worse Five roentgen rayings Improved Later operated and died
No 559 Mr W S Age, 27 Duration, 1 year	3/25/20 5/24/20 6/14/20 7/7/20 9/15/20 1/6/21 2/10/21 5/26/21 2/14/22	67 63.5 70 73 74.5 70 68 64 72	120 100 84 92 72 84 84 62 68	+97 +76 +43 +18 +51 +49 +17 +37	2 2 2 2 3 3 3 3	Mar 25, Apr 14, May 4, 1920 May 24, 1920 June 14, 1920 July 7, July 28, Aug 25, 1920 Mar 28, Apr 18, May 9, 1921	++ ++ Very slight Very slight	++ ++ Less Same Very slight	++ ++ Less Same 0	Moderately severe Improved Stationary Much improved Back at work City fire department Work excessive last week Clinically nearly well		
No 566 Mr B K Age, 42 Duration, 5 years	4/2/20 7/24/20 10/1/20 1/12/21 12/15/21 5/16/22	42.5 47 49 51 55 56	94 72 88 72 62 63	+38 +7 +15 +4 -8 -13	1 3 3 3 3 3	Apr 10, May 1, 22, June 12, July 2, 1920	Very slight Same 0 0	Very slight Same 0 0	++ + 0 0	Mild ease Much improved Slight recurrence of symptoms Clinically well Well except for hypertension		
No 575 Mrs R H Age, 36 Duration, 6 mos	4/8/20 6/29/20 8/16/20 9/17/20 6/7/21 1/20/22	61.5 69.5 71 69 64 66	112 72 68 66 68 62	+32 -15 -20 -13 -8 -11	3 3 3 3 3 3	Apr 8, Apr 26, May 17, June 7, 1920	++ +	++ +	+ 0 0	Mild ease No hyper, suggestion of hypothyroidism Clinically myxedema On thyroid, 3 gr per day for 1 month No further treatment Clinically well		
No 576 Mrs K O Age, 28 Duration, 6 mos	1/9/20 6/30/20 8/16/20 10/26/20 12/1/20 2/3/21 4/2/21 6/22/21 12/1/21 1/21/22 2/9/22 2/13/22 2/14/22	51.5 56.5 61 60.5 60.5 58.5 57 56.5 62.5 60 58.5 58 58	144 124 124 102 124 114 106 120 136 102 121 114 106	+60 +49 +34 +31 +45 +27 +29 +53 +40 +50 +32 +29 +28	2 2 2 2 2 2 3 3 3 3 1 1 1	Apr 9 Apr 30, May 21, June 11, 1920 June 30 July 21, 1920 Aug 18, 1920 Jan 19 1921 Feb 9, Mar 2, 1921 Apr 20, June 15, 1921 July 6, 1921 Dec 1, Dec 8, Dec 21, 1921	Very slight 0 +	Very slight Less Same Same Same	++ + + ++ ++	Moderately severe Somewhat better Much improved Improvement continues Not so well Still thyrotoxic after 16 roentgen rayings Sent into hospital for operation Operation postponed because of im provement without it		
No 577 Mrs T R Age, 50 Duration 3 mos	1/9/20 4/17/20 5/1/20 9/15/20 12/15/20 3/10/21 5/3/21	50 48 48 57 58 52.5 49.5	118 100 96 78 80 88 92	+39 +22 +20 +7 +6 +16 +17	1 1 1 3 3 3 3	Apr 12 1920 May 3, 1920 May 24, June 14, July 11 Aug 4, 25, 1920	++ + + Very slight 0	0 0 0 0	++ 0 0 0	Mild ease without eye signs Much unimproved Clinically not thyrotoxic Same Some evidence of ehr nephritis		
No 591 Miss R F Age, 22 Duration, 3 mos	1/22/20 6/25/20 9/22/20 12/6/20 2/24/21 4/22/21 6/21/21	46 48.5 48 49 50.5 49 51	102 80 86 90 88 100 80	+40 +16 +13 +26 +23 +18 +25	2 2 3 3 3 3 3	Apr 22, Apr 29, May 13 June 1, 1920 Dec 30, 1920 Jan 19 Feb 9, 1921 Mar 2, Mar 20 Apr 20, 1921 May 25, June 15, 1921	++ + ++ ++	Very slight Less Same Same	++ + ++ ++	Moderately severe Improved Not so well Same Subjectively better Tonsillectomy 1 month ago		



TABLE 1—DATA ON EXOPHTHALMIC GOITER CASES—(Continued)

Lab No. Age Duration of Disease	Date	Weight, Kg	Pulse	Basal Metabo- lism, %	Acti- vity	Röntgen Ray Treatments Dates	Goiter	Exoph- thalmos	Tumor	Cardiac Condition	Remarks
No 501— Cont	10/28/21 1/27/22	52	98	+30	3	July 6, 1921	+	Less	+		Still thyrotoxic 13 roentgen rayings Operation advised Writes much improved following operation
No 603 Miss M M Age, 21 Duration, 1 mo	5/1/20 5/14/20 5/28/20 6/18/20 7/30/20 9/30/20 12/8/20 12/18/20 1/12/21 2/12/21 3/21/21 4/27/21 5/14/21 6/14/21 8/3/21 9/21/21 10/25/21 1/24/22 4/20/22	56 57 54.5 57 58.5 64.5 63.5 61 62 64 66 66.5 67.5 68.5 65.5 67 68 64.5 65	120 132 118 100 112 104 120 130 122 123 130 112 108 104 99 102 94 83	+68 +58 +55 +35 +30 +24 +50 +49 +45 +52 +36 +29 +20 +26 +18 +21 +32 +31 +12	3 3 1 1 1 2 2 1 2 2 2 2 2 2 2 2 2 2 3	May 18, 1920 June 8, 1920 June 28, 1920 July 21, Aug Nov 3, 1920 Dec 22 1920 Jan 12 Feb Feb 23 Mar Apr 6 1921 Apr 27, 1921 June 15, July 6, 1921 Feb 15, Mar 8, Mar 20, 1922	+	0	0 ++	Not + syst mur          Normal	Chimically only mildly thyrotoxic  No improvement Slight improvement Worse Much palpitation  About the same condition  Thyroidectomy May 18 Palpitation +, otherwise feels well Frequent and palpitation ++  Clinically well Working  Moderately severe Symptoms more intense Subjectively better Not so well Worse 9 roentgen rayings to date On February 10, sup arteries ligated On February 24 left hemithyroidectomy On April 14, partial right thyroidectomy Much improved Clinically well Clinically well
No 621 Mrs W M Age, 32 Duration, 10 mos	5/20/20 6/9/20 8/14/20 9/16/20 11/3/20 12/3/20 1/3/21 2/5/21 2/18/21 3/5/21 4/22/21 7/20/21 10/20/21 5/11/22	56.5 57.5 58.5 58.5 54 53 54 54 54 52.5 58.5 59 58.5 55	120 110 116 96 112 104 132 120 108 112 92 76 71 75	+74 +46 +50 +30 +35 +68 +61 +61 +65 +48 +40 +13 +9 +12 +14	2 1 2 2 2 2 2 2 1 1 1 3 3 3	June 9, June 30, July 21, 1920 Sept 1, 1920 Sept 22, Oct 13, 1920 Nov 3 Nov 24, 1920 Dec 13, 1920	++ +	+	+++ ++	Not + syst mur	
No 628 Mrs M J Age, 41 Duration, 10 years	5/27/20 11/16/20 1/3/21 2/2/21 3/23/21 5/4/21 1/6/22 3/9/22 4/14/22 5/17/22	49.5 48 48.5 50.5 53 51.5 54 55.5 55.5 55	120 106 132 105 94 88 96 111 90 67	+57 +65 +49 +11 +18 +9 +15 +22 +10 -10	3 3 3 3 3 3 3 3 3 3	Nov 17, Dec 1, Dec 22, 1920 Jan 12, 1921 Feb 2, Mar 23, 1921 Apr 13, 1921 June 28, 1921 Mar 14, Apr 5, 1922	++ +	+	+ 0	Not + syst mur	Moderately severe No treatment since first note  Improved Improved A little more palpitation Objectively improved

No 677 Mr H B Age, 43 Duration, 4 mos	6/22/20 7/3/20 10/6/20 12/1/20 1/6/21	66 65 66 72 72	92 104 100 74 54	+33 +33 +27 +20 +30	2 1 3 3 3	June 28, 1920 July 21, Aug 11, 1920 Nov 3, 1920 Dec 1, 1920, Jan 1, 1921 Jan 26, Feb 16, 1921	+ Less  Same  Very slight	+ Less  Same  Very slight	+ Less  Same  Very slight	Enlarged flabbating Same  Same  Same	Mild, but with thyroid heart  Thyroid symptoms nearly gone Car diac unchanged On digitals On digitals On digitals Quinidin fails to restore normal rhythm
No 728 Miss B M Age, 49 Duration, 10 mos	9/16/20 10/28/20 1/13/21 3/31/21 5/12/21 8/24/21 1/26/22	65.5 70.5 76 72 77.5 79 81.5	110 82 80 100 70 76 78	+41 +19 +16 +28 +1 -11 +9	3 3 3 3 3 3 3	Aug 18, 1920 Sept 16, Oct 7, 1920  Mar 31, Apr 21, 1921	+ + Less 0 0	+ Less 0 0	+++ 0 0 0	Not + syst mur Normal Normal	Moderately severe Stationary Much improved  Clinically well Clinically well
No 762 Mrs M II Age, 28 Duration, 3 yrs	10/12/20 10/26/20 11/9/20 2/1/21 5/3/21 5/28/21 6/10/21 10/15/21 1/19/22 2/7/22 2/17/22 4/18/22	44 44 46 48.5 49 48 48 49.5 50.5 50 49.5 53	126 102 100 102 100 88 96 77 96 98 99 76	+67 +47 +45 +42 +37 +31 +27 +15 +38 +31 +13 -2	1 1 2 2 2 1 1 2 2 1 1 2	Oct 18, 1920 Nov 10, Dec 10, 1920 Feb 23, Mar 16, Apr 6, Apr 27, 1921	++ +  Left ++ Left larger	++ +  ++	++ ++  ++	Normal   Slightly +	Moderately severe Symptoms increasing Slight improvement Still thyrotoxic after 7 roentgen rays On May 31, right hemithyroidectomy Still appears thyrotoxic Worse Two months pregnant Second operation advised On February 10, partial left lobectomy Pregnancy continuing
No 767 Mrs L L Age, 45 Duration, 1 year	10/20/20 2/3/21 3/2/21 6/1/21 8/3/21 1/23/22	57 61 61.5 60.5 63	88 82 88 88 88	+41 +11 +21 +23 +28	2 2 2 3 3	Oct 20, Nov 17, Dec 15, 1920, Jan 5, Feb 2, 1921 Mar 2, 1921 June 1, 1921	++ ++    	++ +    	+++ ++  0	Moderately severe Much Improved  Subjectively well Writes that she is well	
No 750 Mrs I M Age, 35 Dur., 1 yr	10/29/20 1/5/21 3/23/21	49 48.5	120 120	+85 +61 +50	3 3	Nov 3, Nov 24 Dec 15 1920 Jan 5, Jan 26, Feb 16, 1921	++   	++   	++   	Normal	Data supplied by Dr Frank H Lacey He operated later
No 798 Miss A R Age, 17 Duration 1 yr	11/19/20 1/19/21 3/3/21 4/14/21 11/1/21 3/17/22	63.5 61 61 60.5 61 55.5	120 96 78 110 74 62	+40 +7 +6 +14 +8 +4	3 3 3 3 3 3	Nov 19, Dec 8, Dec 29, 1920 Mar 4 1921	++ ++ ++ ++ ++ +	++ + + Less	++ + 0 0 Very slight	Normal	Moderately severe Much improved Clinically well Goler still present No symptoms except a little palpitation Essentially well
No 802 Mrs P S Age, 26 Duration, 15 mos	11/15/20 11/29/20 1/24/21 3/16/21 7/1/21 11/2/21 5/10/22	68.5 65.5 71 72.5 73 65.5	124 120 66 84 104 82 79	+82 +75 +27 +9 +40 +3 +10	3 1 3 3 3 3 3	Nov 30, Dec 22 1920 Jan 20 1921 Feb 9, 1921	++  + Less	++  + Less	++  0 0	Not + syst mur	Moderately severe Improved Much improved Getting obese Clinically well 14 months pregnant Clinically well Normal delivery Mar 27

TABLE 1—DATA ON EXOPHTHALMIC GOITER CASES—(Continued)

Lab No., Age Duration of Disease	Date	Weight, Kg	Pulse	Basal Metabo- lism %	Activ- ity	Röntgen Ray Treatments Dates	Goiter	Exoph- thalmos	Tumor	Cardiac Condition	Remarks
No 803 Miss P S Age, 35 Duration, 6 mos	11/16/20	71	112	+58	2	Nov 18, Dec 9, Dec 29 1920 Jan 20, Feb 9, 1921 Mar 2, Mar 24, Apr 14, 1921	+	+	+	Normal	Recent mild ease Slight improvement Slight improvement More improvement Much improvement Clinically well
	12/30/20	71	116	+51	2		+	+	Less		
	3/ 2/21	74	98	+31	2		0	Less	0		
	5/ 1/21	76.5	86	+10	2		0	Very slight	0		
	11/ 7/21	80.5	90	+15	2		0	Very slight	0		
No 805 Mrs I C Age, 41 Duration, 8 mos	3/ 7/22	76	82	+10	3					Normal	
	11/18/20	66.5	94	+24	2	Dec 8, Dec 29, 1920 Jan 19, 1921 Feb 9, Mar 2, 1921	+	+	+	Slightly + syst mur	On April 1, 1921 operation, Dr Libbey Writes that she is greatly improved
	1/31/21	66.5	112	+23	2						
No 817 Mr F B Age, 42 Duration, 2 years	4/ -/21			+12							
	2/ 6/22										Mild ease
	12/ 3/20	59	100	+47	2	Dec 8, Dec 29 1920, Jan 19, 1921 Feb 2, Mar 16, June 8, 1921 June 29, Aug 17, Sept 7, Oct 5, 1921 Apr 26, May 17, 1922	+	+	+	Enlarged	Symptoms much less marked
	2/ 2/21	59	100	+54	2			Less	Less		
	6/13/21	58	92	+33	2		Less		0	Normal	
	10/10/21	56	74	+24	2						Very toxic and acute case Improved Symptoms much less severe
	1/23/22	56.5	77	+30	2						
	4/26/22	54.5	91	+38	2						Partial thyroidectomy 7 years ago
	5/31/22	53.5	93	+35	2						
No 818 Mrs A M Age, 46 Duration, 8 mos	12/ 3/20	31.5	124	+81	1	Dec 15, '20, Jan 6, 20, Feb 9, Mar 2, 23, '21 Apr 23, May 11, 1921 June 1, June 22, Aug 17, Sept 28, 1921	++	++	+++	Not + syst mur	Much improved Not so well Much improved
	4/18/21	42	100	+62	1						
	5/26/21	45	106	+49	2		Less	+	+	Normal	
	1/27/22	46	96	+44	3					Enlarged fibrillating	
No 819 Mrs A A Age, 44 Duration, 8 years	12/ 4/20	60	100	+50	1	Dec 8, 1920 Jan 6, Jan 26, Feb 16, Mar 9, 1921 Nov 18, Dec 7, 1921, Jan 5, 1922	++	+	+	Not so large normal rhythm	Much improved
	12/14/20	60	100	+38	1						
	3/15/21	61.5	96	+6	2						
	6/ 4/21	64.5	76	+5	3						
	11/ 4/21	69	98	+31	3						
	11/18/21	69	96	+32	3					Normal size and rhythm	
	1/25/22	70	66	-6	3		+	Very slight	0		

No 866 Miss M K Age, 17 Duration, 1 year	1/25/21 7/21/21 11/ 2/21 12/ 7/21 2/19/22 3/24/22	51 52.5 63.5 63 57 56	120 112 60 75 91 86	+23 +37 -17 -1 +18 +18	2 1 2 2 2 2	Aug 17, Sept 21, 1921  Feb 25, Mar 15, Apr 26, 1922	+	+	+	0	Not + syst mur	Mild degree of hyperthyroidism Much improved Suggests myxedema Thyroidectomy on February 2 Not so well Considerable palpitation
No 909 Mrs K K Age, 23 Duration, 5 years	2/19/21 4/ 2/21 4/11/21 10/11/21 12/16/21 3/ 1/22	68.5 67.5 64.5 63 65.5 68.5	108 118 108 109 72 92	+22 +26 +39 +38 +1 +4	2 1 1 1 3 3	Oct 19, Nov 9 Nov 23, Dec 14, 1921	+	+	+	0	Enlarged	Hyperthyroidism slight Gouter heard No improvement on rest Roentgen ray treatment advised Much improved
No 933 Mrs C S Age, 40 Dur, 1 yr	3/16/21 5/13/21	58.5 60.5	100 102	+55 +47	1 2	Mar 18, Apr 13, May 4, 1921 May 25, June 22	+	+	+	+	Normal	Moderately severe Not much change
No 934 Mrs M R Age, 34 Duration, 6 mos	3/17/21 6/23/21 10/19/21 11/30/21	57.5 55.5 58 58	124 122 117 121	+73 +65 +59 +69	2 2 2 2	Mar 30, Apr 20, May 12, June 1, June 22 Aug 17, Sept 7, Sept 28, 1921 Oct 19, Nov 9, 1921, Jan 4, 1922	+	+	+	++ ++	Slightly + syst mur	Moderately severe, acute case Slight improvement only Operation advised
No 937 Mrs M H Age 23 Duration, 6 mos	3/18/21 3/23/21 6/15/21 11/ 5/21 3/17/22	48 48 51.5 54	134 116 92 101	+61 +46 -2 +13	1 1 2 3	Mar 22, 1921 Apr 13, May 4, May 25, 1921	++ +	++ +	++ +	++ Very slight	Normal Normal	Moderately severe, acute case Much improved Writes that she is 'feeling fine'
No 944 Mrs F P Age, 45 Dur, 1 yr	3/22/21 8/ 2/21 9/15/21	56.5 51 59	112 100 119	+58 +39 +39	2 2 2	Aug 6, Aug 24, Sept 14, 1921 Oct 5, Oct 26 Nov 16, 1921	+	+	0 +	++ +	Normal	Moderately severe No improvement Operation advised
No 957 Mrs F A Age 30 duration, 1 year	3/31/21 4/ 7/21 6/15/21 10/28/21 1/ 6/22 3/ 8/22	50 50 55 57 56 57	124 105 96 104 104 81	+71 +49 +29 +22 +34 +15	1 1 3 3 3 3	Apr 6, 1921 Apr 27, May 18 June 8 1921 June 2) Aug 17 Sept 7, Sept 28, 1921 Jan 11, Feb 1 Feb 23 1922	++ ++ ++ ++ +	++ ++ ++ ++ +	++ ++ ++ ++ +	++ ++ ++ ++ +	Not + syst mur  Very slight 0	Moderately severe Much improved Much improved Much improved Gouter and nephritis remains

TABLE 2—DATA ON TOXIC ADENOMA CASES

Lab No., Age, Duration of Disease	Date	Weight, Kg	Pulse	Basal Metabo- lism, %	Acti- vity	Röntgen Ray Treatments Dates	Goiter	Tremor	Cardiac Condition	Remarks
No 26 Mrs F A Age 33 Duration, 6 mos	6/22/15 4/ 9/19 2/26/20	60 59.5 60	97 107 108	+23 +52 +28	3 3 3	Feb 27, Mar 20, Oct 29, 1918 Feb 26, Mar 22, Apr 12, 1920	0 + 0	0 + +	Mild disease	Diagnosis made of organic heart disease Developed definite clinical signs of hyperthyroidism Slight improvement
No 313 Miss V G Age, 21 Duration, 4 mos	8/13/19 8/19/19 8/30/19 11/24/19 12/ 1/19 3/15/20 12/ 2/21	40.5 40 39.5 40.5 40.5 41	113 93 104 92 90 92	+71 +66 +48 +37 +28 +38	1 1 1 3 3 3 3	Sept 15, Oct 11, Nov 3, 1919 Nov 24, 1919 Mar 15, Apr 5, Apr 26, 1920	Rt ++ + 0	+	Normal	Moderately toxic
No 333 Miss A H Age, 32 Duration, 4 years	9/30/19 10/ 8/19 11/10/19 2/ 2/20 3/19/20 7/14/20 9/20/20 4/27/21 12/12/21 3/14/22	56 55 58 57 58.5 60.5 56 60.5 60	120 104 100 100 104 100 100 85 86	+63 +53 +40 +42 +34 +27 +24 +31 +17 +18	1 1 2 2 2 3 3 3 3 3	Oct 8, Nov 3, 1919 Nov 24, Dec 15, 1919, Jan 12, 1920 Feb 24, 1920 Mar 24, Apr 14, May 5, 1920	++ + + 0 0	+	Normal	Moderately toxic, getting worse
No 348 Mrs M B Age 38 Duration, 1 year	10/ 7/19 12/15/19 2/25/20 9/29/20 2/25/21 8/29/21 9/15/21 10/31/21 1/10/22 3/ 7/22	39 42 47 48.5 50.5 48 45.5 46 46	116 100 80 66 64 64 61 60 63 57	+50 +52 +18 -3 -6 -35 +2 -13 -1 0	3 3 3 3 3 3 3 3 3 3	Oct 7, Oct 27, Nov 19, 1919 Dec 15, 1919, Jan 5, Jan 26, 1920	+	++ 0 0 0 0	Slightly + syst mur	Moderately toxic Much improved Clinically well Remained well Skin a little dry Became myxedematous Started on thyroid Returned to normal appearance on thyroid
No 440 Mrs A D Age, 39 Duration, 3 years	12/ 9/19 3/16/20 2/ 3/22	53 53.5 54.5	105 96 87	+23 +11 +11	3 3 3	June 23, July 28, Aug 19, Nov 17, 1919 Dec 8, Dec 29, 1919	+ + Less	+	Normal Normal	Slightly toxic Clinically well
No 456 Mrs J F Age, 52 Duration, 2 years	12/20/19 3/13/20 6/ 3/20 8/ 2/20 9/20/20 2/ 4/22 5/ 5/22	46 48 48 46.5 46.5 46 46	118 120 120 110 108 106 93	+45 +45 +31 +23 +15 +35 +8	2 2 2 2 2 3 3	Apr 1, Apr 22, May 12, 1920 June 3, June 24, 1920 Aug 2, Aug 23, 1920 Mar 3, Mar 24, Apr 14, 1922	+	+	Moderately +	Mild, stationary case Adenoma removed 1 month ago Hypertension No treatment No improvement Clinically much improved Slight return of nervousness Moderate improvement



This chart is made in a somewhat peculiar way We wished to get all available cases into the early portion of the curve, but it will be noted that some drop out from time to time, so that fewer cases were used in the later than in the earlier portion of the curve

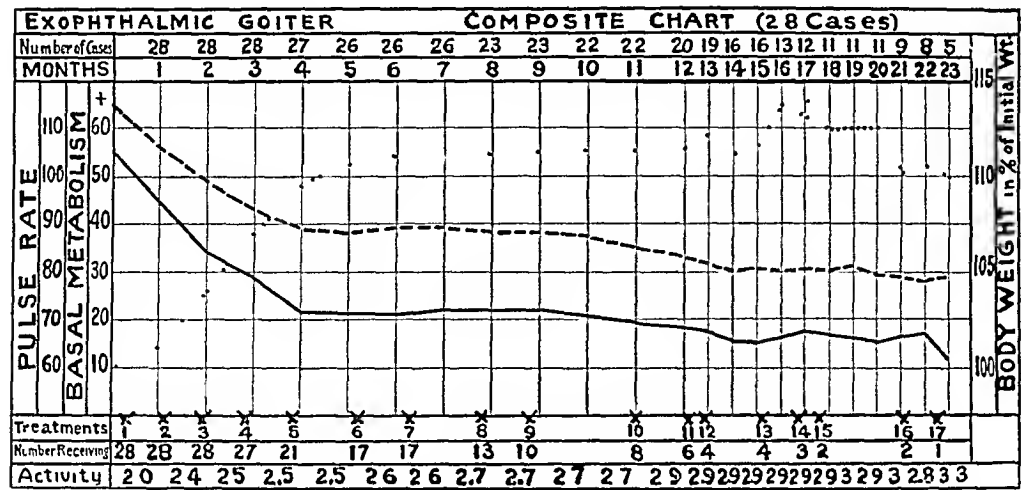


Fig 1—In this and in all the other charts, the perpendicular rulings are at intervals of one month The solid black line denotes basal metabolism (per cent variation from Sage Institute standards), the interrupted line represents the pulse rate, and the dotted line represents body weight In Figures 1 to 5 the weight is expressed in per cent of the initial weight which is taken as 100 per cent Figures 1 to 5 are composite, the remaining figures are individual charts Roentgen-ray treatments are denoted by X Activity in Figures 1 to 5 is shown in the following manner 1, denotes complete rest in bed, 2, partial rest, 3, following usual occupation For the composites these figures for all individuals composing the composite are averaged

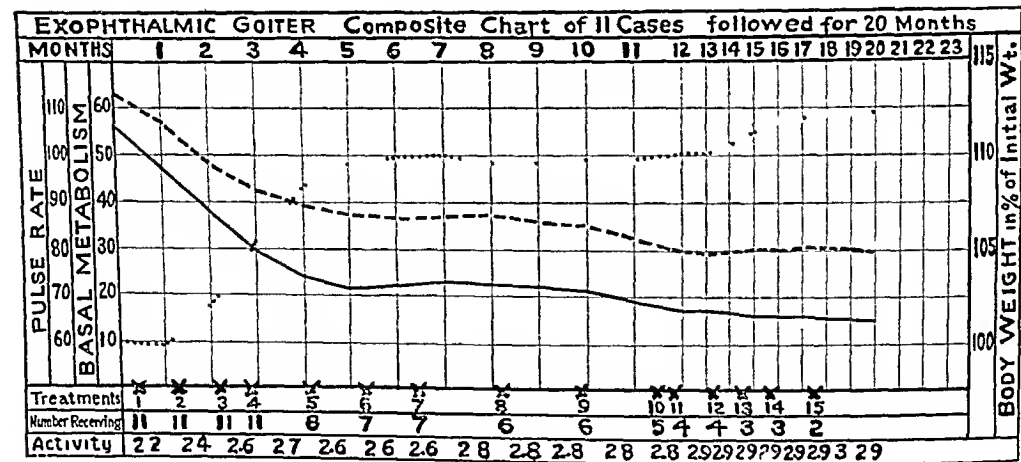


Figure 2

To answer what might be an objection to this method of charting, we have in Figure 2 shown the composites of the eleven cases in which our data run through twenty months It is interesting to note that this chart is nearly identical with the first The drop in this instance in

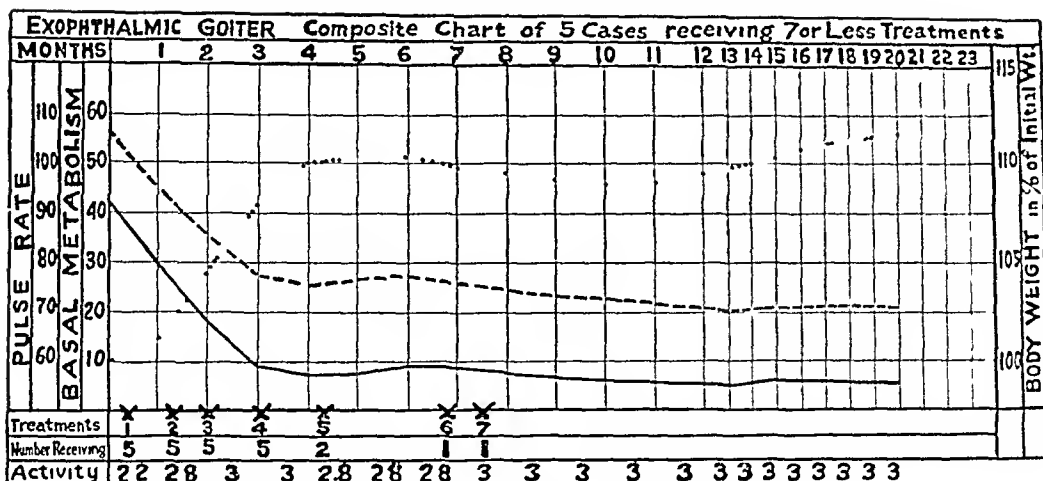


Figure 3

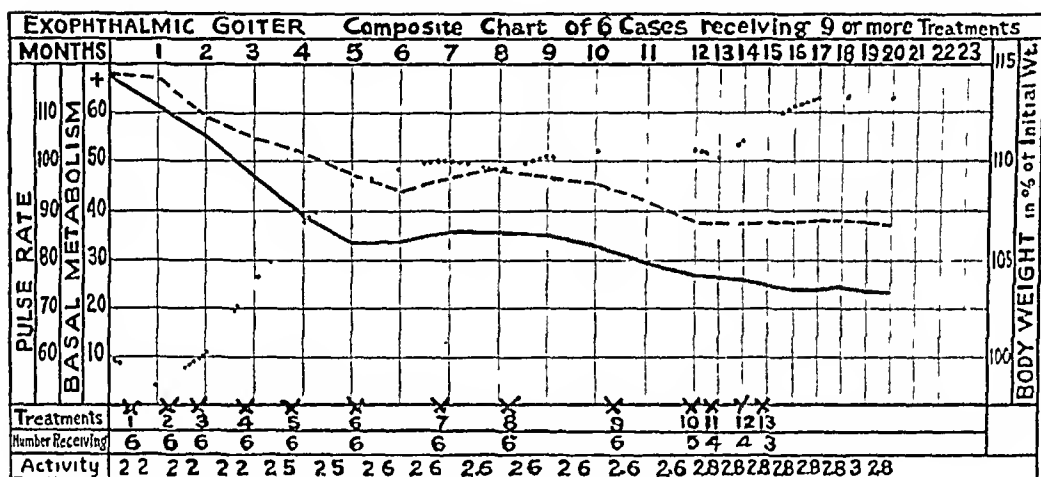


Figure 4

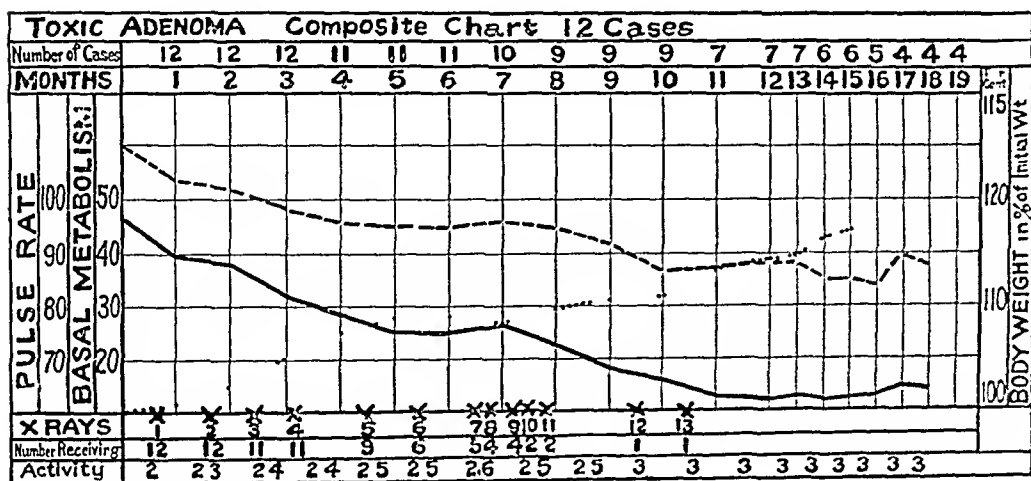


Figure 5



four months is in the pulse, from 113 to 89, and in the metabolism, from  $+56$  to  $+24$  per cent. The weight increase was 8 per cent. A further drop of 2 or 3 points occurred in the fifth month, and then there is the same plateau seen in Figure 1.

To get some idea of the relation of the number of treatments to the effect, we have separated the cases shown in Figure 2 into a group (Fig. 3) of patients receiving seven treatments or less, and those (Fig. 4) receiving nine treatments or more.

Both these charts are similar in general contour to the previous ones. The cases averaged in Figure 3, receiving the smaller number of treatments, are not unnaturally the milder ones. In this group the pulse and metabolism both assume normal levels at the end of four months, the former falling from 107 to 75 and the latter from  $+43$  to  $+7$  per cent. Furthermore, they stay at these normal levels through the twentieth month.

In the more severe group, shown in Figure 4 and receiving more treatment, there are similar drops in pulse and metabolism curves and rise in the weight curve. The drops in the first two, however, do not bring them by any means to a normal level, the pulse falls from 118 to 97 and the metabolism from  $+68$  to  $+34$  per cent in the first five months. From then on, through the next fifteen months, there is only a further drop of 10 points in pulse and metabolism in spite of continued roentgen-ray treatment.

**RECENT SERIES** *Toxic Adenoma*—Turning now to the cases of toxic adenoma we find that all the patients showed improvement with roentgen-ray therapy and five were apparently cured. The composite curves are shown in Figure 5.<sup>37</sup> The character of the curves is quite different from that of the exophthalmic goiter patients. The drop in pulse and metabolism is far more gradual. So, too, is the gain in weight. Nevertheless, in the group as a whole a normal pulse and metabolism level is finally reached.

**PREWAR SERIES** *Exophthalmic Goiter*—In the report published in 1919 by Means and Aub<sup>3</sup> were given the data on fifteen patients with exophthalmic goiter treated by roentgen ray alone. We have attempted to get end result data in all of these cases. Three patients have been lost, three have died, the remaining nine have been to the laboratory this spring (1922).

A summary of the data already published for these, together with the data just received, is given in Table 3.

It will be noted that six of the nine patients have normal metabolic rates five or six years after their first treatment, another has a slight

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<sup>37</sup> Two cases in Table 2 are not included in the composite because of insufficient data (Cases 26 and 440).

elevation, + 15 per cent. She, however, had no clinical symptoms or signs and like the six with normal rates was apparently in good health. Two others still had elevated metabolism and clinically were better but not well. Both patients had been advised to submit to an operation in 1919 but had refused.

#### V ILLUSTRATIVE CASES

We have previously emphasized the importance of the chart in following the progress of toxic goiter or myxedema,<sup>2, 31</sup> and pointed out that with the patient with thyroid disease the clinical chart serves the same purpose that it does in the fever patient. In thyroid disease, however, we plot not pulse, temperature and respiration, but metabolism, pulse and weight.

TABLE 3—DATA ON CASES PREVIOUSLY PUBLISHED

Laboratory Number	Number of Roentgen Ray Treatments	Date of First Treatment	Date of Last Treatment	Basal Metabolism						
				Basal Metabolism Before Treatment	One Year After First Treatment	Two Years After First Treatment	Three Years After First Treatment	Four Years After First Treatment	Five Years After First Treatment	Six Years After First Treatment
12 Mrs. T. W.	6	1/26/16	8/31/16	+71, +49	+46					+40
25 Mrs. A. L.	14	6/24/15	2/15/18	+63	+61					+4
33 Mr. B. S.	6	10/13/15	7/ 5/16	+78	+14	+63		+14		+1
48 Mrs. E. N.	13	1/12/16	11/ 3/17	+82	+54		-14			+1
58 Mr. R. S.	7	2/16/16	6/ 6/16	+48	+49	+13	+27	+16	+7	+1
66 Miss F. C. C.	11	8/29/16	7/ 7/17	+42	+28	-6			+5	0
110 Miss S. E. M.	6	11/28/16	3/30/17	+34, +42	-1	+15			+5	
122 Mrs. C. M.	6	1/ 2/17	5/ 5/17	+89, +74	+66	+39		+43	+3	
135 Mrs. V. M. D.	7	4/ 2/17	1/ 3/18	+39, +22	+25	+4			+3	
				+28, +47						

We cannot conveniently give the charts of the fifty-eight cases in the present series, certain of them have appeared elsewhere,<sup>2, 4, 6, 31</sup> others we will give now, and for the remainder the reader is referred to Tables 1 and 2, which contain all the essential data, though not in graphic form.

The charts shown here are chosen to illustrate certain type reactions and special points.

We will discuss, first, the findings in three patients who responded very favorably to roentgen-ray therapy.

#### REPORT OF CASES

CASE 376—Mrs. R. N., a Jewess, aged 27, had had toxic symptoms for one year and a goiter for four months. The symptoms began after an attack of influenza. She had had no treatment previous to her first visit to the hospital. She had slight, but definite, eye signs, slight soft symmetric enlargement of the thyroid with bruit, and a slight tremor. It was felt that she had typical but

not more than moderately severe exophthalmic goiter She has received no treatment except nine irradiations She has even kept at her usual mode of life—housewife—and has done her work as usual

Her chart is shown in Figure 6 Her metabolism began to drop after four treatments and reached normal after nine The curve stayed at the normal level for the next eighteen months, and she has been relieved of all symptoms To date, it seems to be a complete cure

CASE 803—Miss P S, graduate nurse, aged 35 Trouble began six months before we saw her After getting very tired physically, she developed palpitation, marked asthenia and weight loss She had slight but definite eye signs, slight fullness of the thyroid without bruit, slight but definite tremor and warm moist hands A diagnosis of exophthalmic goiter was made and she was started on roentgen-ray treatment The chart is shown in Figure 7 She gave up her work for the greater part of a year, but in other respects was reasonably active The only treatment was the roentgen-ray As the chart shows, metabolism and pulse

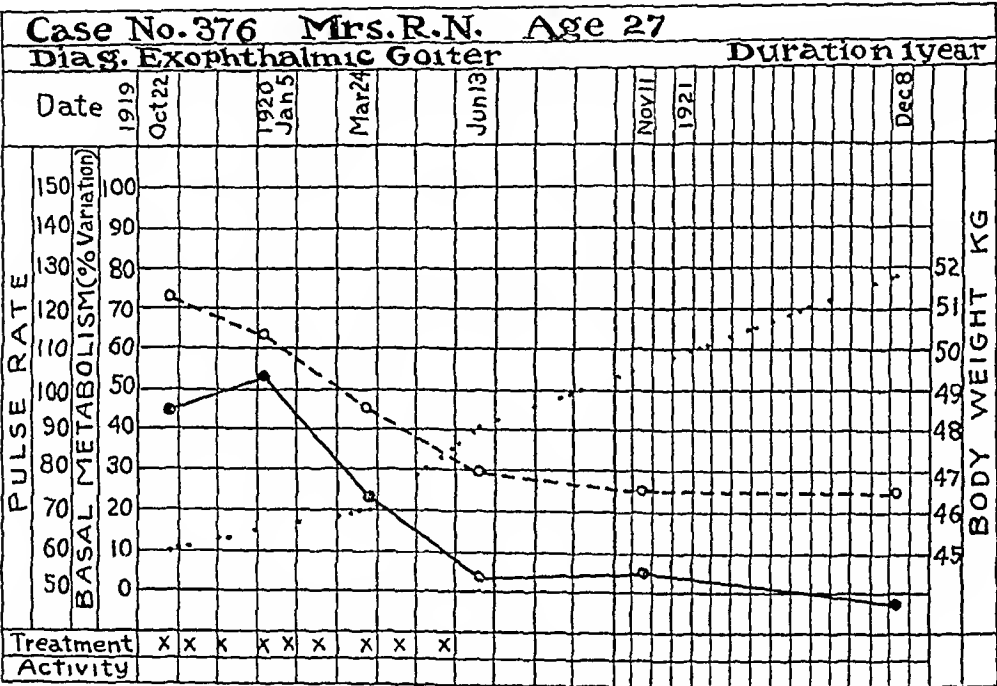


Fig 6—This chart and Figures 7 to 14 inclusive are constructed like the preceding composites, except that body weight is given in kilograms, and activity is shown by shading instead of by numbers, full black = rest in bed, half black = partial rest, all white = usual mode of life

curves reached an essentially normal level in six months and have stayed so for ten months more She has been back at work for four months without ill effect Her work is caring for a psychopathic patient and is not easy

CASE 802—Mrs F S, a Jewess, aged 26, who for eighteen months had exophthalmos, thyroid enlargement and the classical symptoms of hyperthyroidism She had had no treatment when we first saw her A diagnosis was made of exophthalmic goiter of moderate severity, and a course of roentgen-ray treatment prescribed She came into the hospital for a fortnight Her roentgen-ray treatment was started and then she went home and led her usual life The chart (Fig 8) shows a rapid fall in metabolism and pulse, reaching normal in four months, and a marked gain in weight The high result of July 21, 1921, was at a time when she was starting a pregnancy Seen again Nov 2 1921 she was five months pregnant, her metabolism was normal, and everything was going smoothly We heard from her when nearly full term (March 15, 1922),

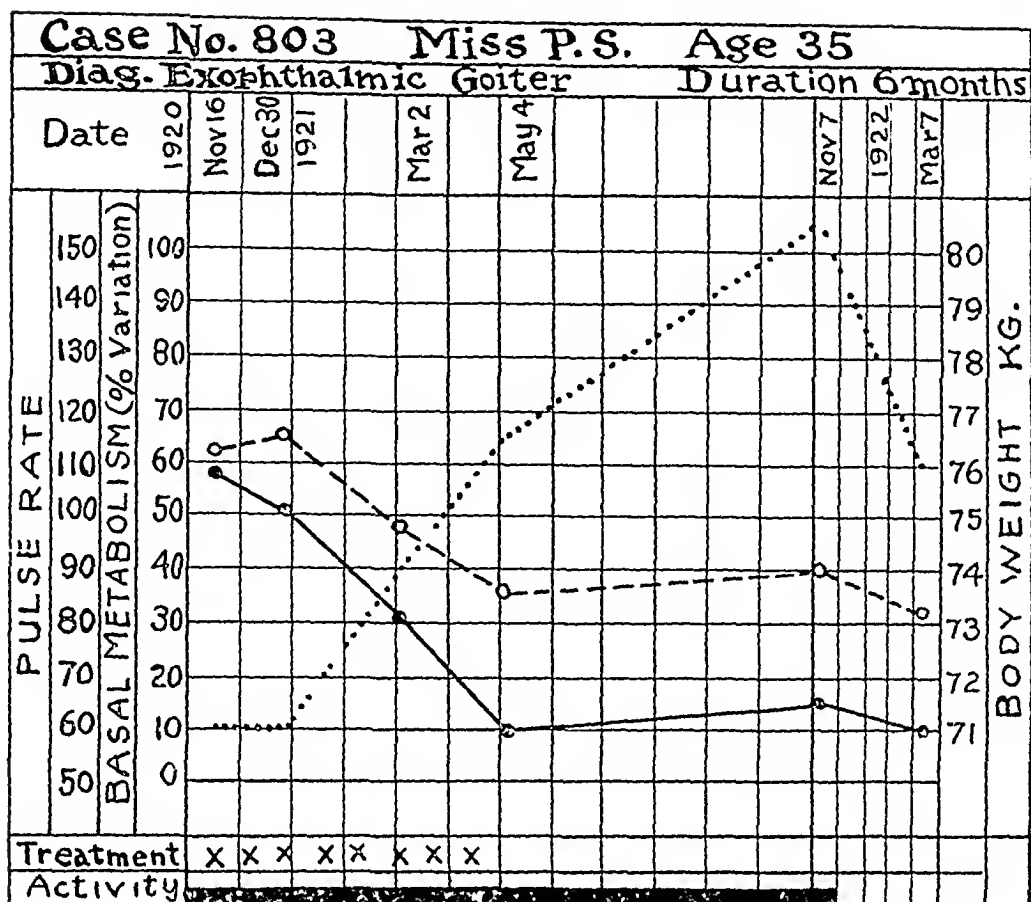


Fig 7—The solid line indicates basal metabolism, interrupted line, pulse rate, dotted line, body weight. Activity is shown by shading, solid black squares indicate rest in bed, half black squares, partial rest, white squares, usual mode of life.

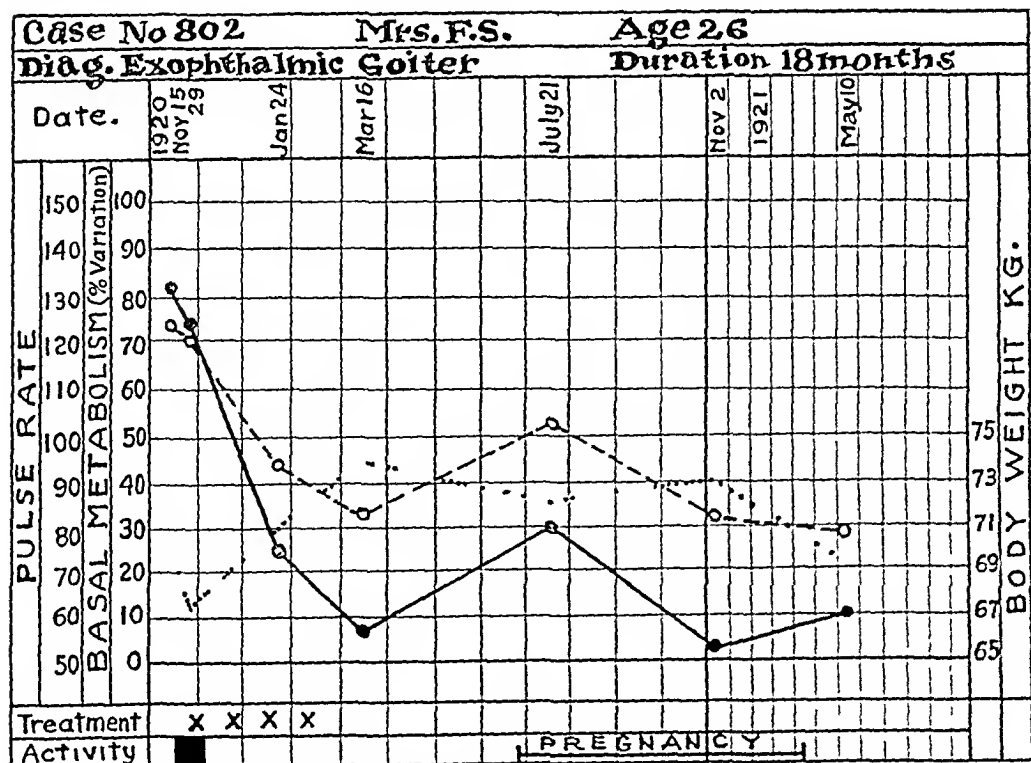


Fig 8—The solid line indicates basal metabolism, interrupted line pulse rate, dotted line, body weight. Activity is shown by shading, solid black squares indicate rest in bed, half black squares, partial rest, white squares, usual mode of life.

and there were still no symptoms referable to hyperthyroidism. Her baby was born at full term on March 27, normal delivery. On May 10 she was clinically well and had a normal metabolism.

The next three cases illustrate improvement under roentgen-ray treatment followed by relapse. The first portion of the story and the charts of two of the patients were published a year ago (June, 1921)<sup>31</sup> The events which have occurred since then in each case are instructive and make it seem worth while to republish the charts, bringing them up to date.

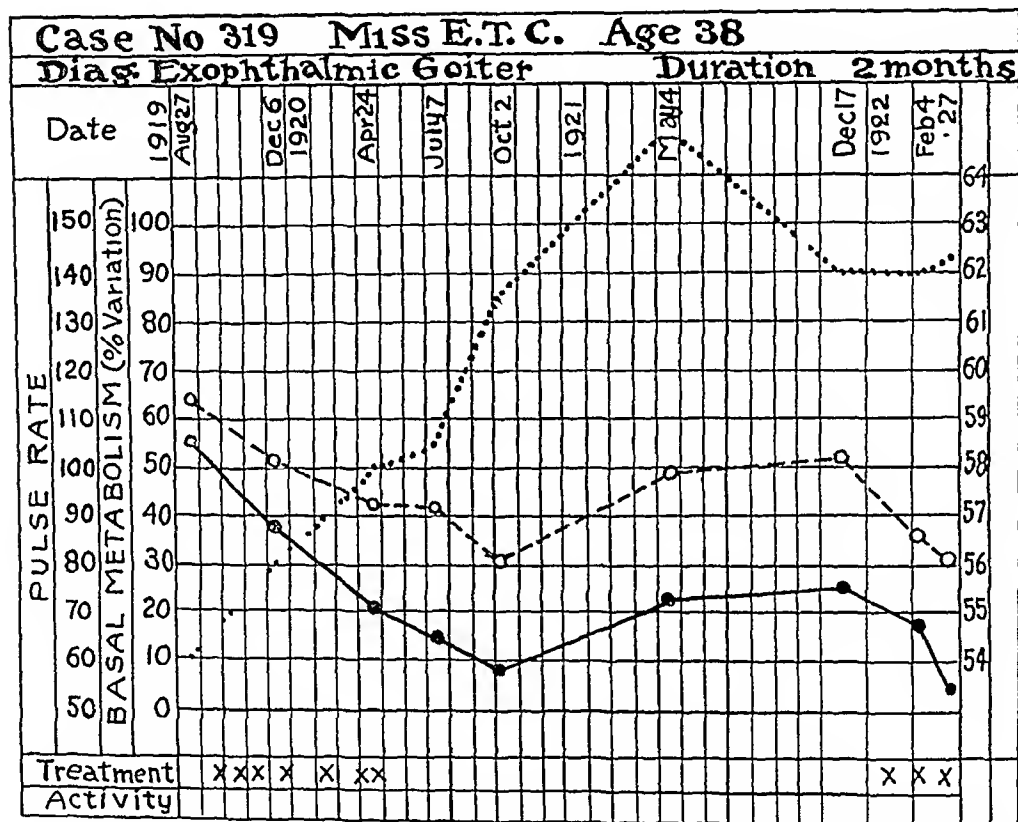


Fig 9—The solid line indicates basal metabolism, interrupted line, pulse rate, dotted line, body weight. Activity is shown by shading, solid black squares indicate rest in bed, half black squares, partial rest, white squares, usual mode of life.

CASE 319—Miss E. T. C., aged 38, with a recent and mild form of exophthalmic goiter. The chart as shown a year ago showed a steady improvement and return to normal under roentgen-ray treatment alone up to the fourteenth month. An observation in the twenty-first month, however, showed a rise. The remark was then made, "This rise may or may not be of importance. But it illustrates the usefulness of the chart, for it puts us on our guard against a possible relapse which we might have missed on the basis of the clinical picture alone," for there were no symptoms at that time. The chart given now (Fig 9) shows that the relapse did materialize, though it was a mild one, and that it is again being controlled by roentgen-ray treatments.

CASE 603—Miss M. M. The chart of this patient when first published showed the events of a year. Now we add a second year. This patient has

always been somewhat atypical, probably a case of exophthalmic goiter, but never showing any eye signs. She responded well to roentgen-ray treatment but relapsed. Last year the remark was made, "A second course of roentgen-ray treatment seems to be relieving this (relapse) much as it did in the first instance." This statement proved to be unduly optimistic, as is shown in Figure 10. A third course of treatment was necessary, but seemed to have the desired effect. She is at last apparently well and has been working for three months.

CASE 411—Mr. A. S., a business man, aged 39 years, showed a rapid improvement with roentgen-ray and then a slight relapse. In November, 1919, he consulted Dr. Edsall, who found that he had typical exophthalmic goiter of moderate severity. The symptoms had been present for but three months at that time. His chart is shown in Figure 11. After the third roentgen-ray treatment he showed a marked clinical improvement, fall in pulse and metabolism and gain in weight. When seen Oct. 22, 1920, he had a slight return of symptoms and an elevation in metabolism. This observation was obtained

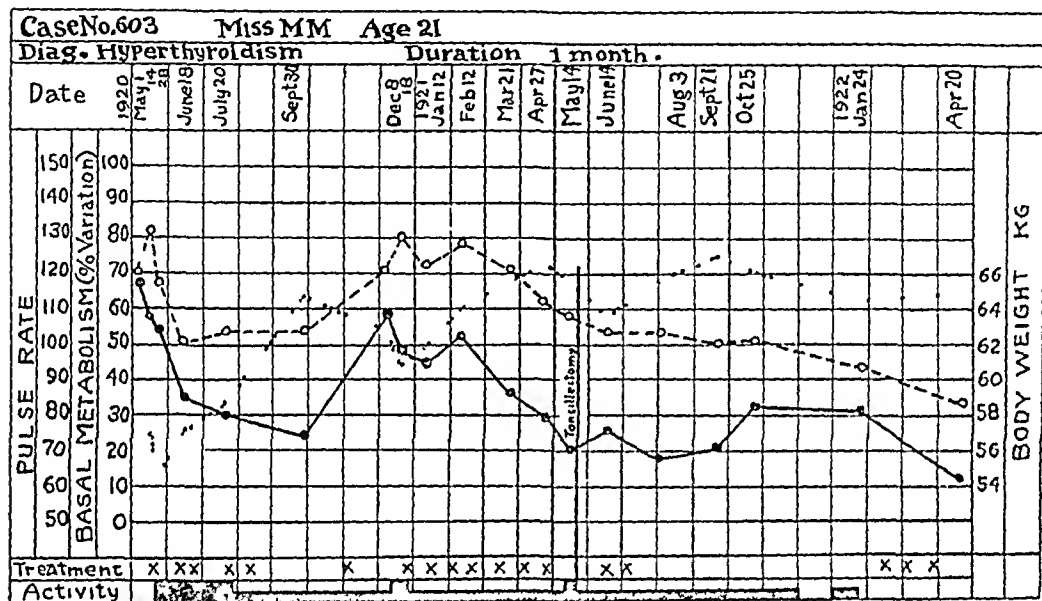


Fig. 10—The solid line indicates basal metabolism interrupted line, pulse rate, dotted line, body weight. Activity is shown by shading, solid black squares indicate rest in bed, half black squares, partial rest, white squares, usual mode of life.

however, at the end of a spell of very hot weather which had used him up a good deal. Jan. 15, 1921, after two more roentgen-ray treatments, he was much better and had returned to work. May 1, 1921, there was again an increase in metabolism and slight return of symptoms. This was during hot spring weather. The last observation was made April 29, 1922. He had worked all winter and considered himself well, except that he still gets tired rather easily. The exophthalmos, the goiter and the tremor had disappeared, and the heart was normal.

CASE 591—Miss R. F., aged 22, with a recent (three months) and mild type of exophthalmic goiter, showed no consistent improvement with the roentgen-ray. Her chart is shown in Figure 12. A slight drop in pulse and metabolism and slight gain in weight, together with a little symptomatic improvement, occurred after four rayings but at the end of the eighteen months she was no better than at the start although she had had a total of thirteen treatments. This was a definite failure of roentgen-ray treatments. We advised her to have an operation and she went to Dr. Frank H. Lacey,

who operated Jan 27, 1922, she wrote us that she was very much improved following the operation

CASE 633—Mrs M M, aged 37, had an adenomatous goiter with hyperthyroidism She had had symptoms of hyperthyroidism for two years when we first saw her Her chart (Fig 13), shows that a first course of treatment caused some improvement Then there was a slight relapse, but a second course brought about an essentially normal state and at the same time the goiter disappeared

Of the prewar series there are two cases in which the recent events are sufficiently interesting to deserve individual note The early histories of both of these have already been published<sup>3</sup>

CASE 48—Mrs E N, aged 30, had had exophthalmic goiter for four and a half years when she first came to us The chart as originally published shows a drop in metabolism of about 20 points coincident with rest in bed and the

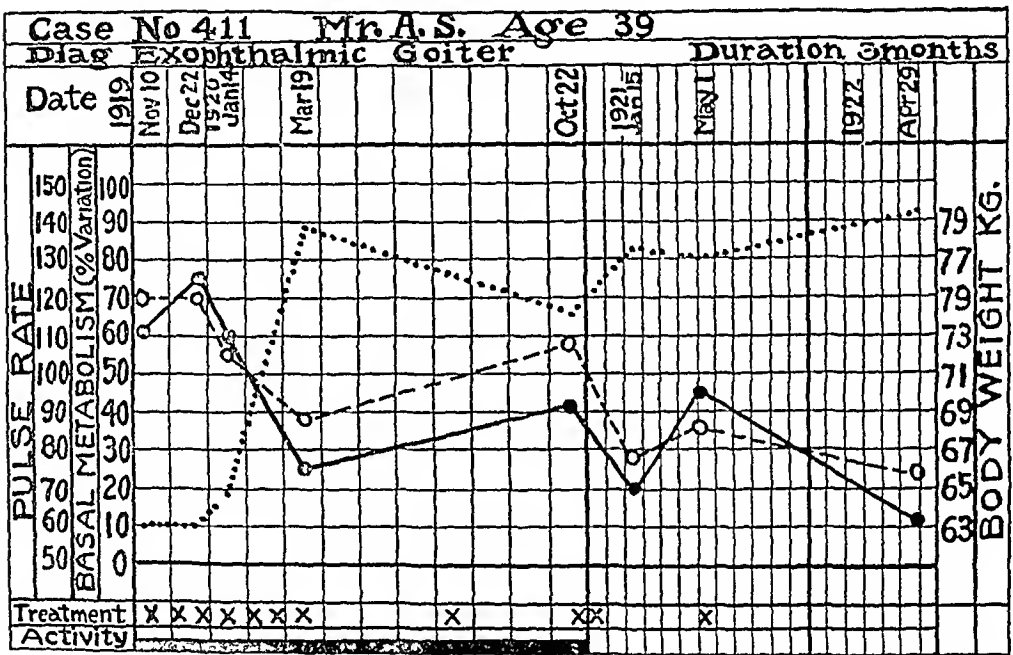


Fig 11—The solid line indicates basal metabolism, interrupted line, pulse rate, dotted line, body weight Activity is shown by shading, solid black squares indicate rest in bed, half black squares, partial rest, white squares, usual mode of life

first two roentgen-ray treatments There was then a period of four months in which there was no treatment but partial rest She gained some weight and her pulse fell somewhat, but her metabolism showed no drop She resumed her work (housewife, family consisted of husband, two children, sister and sister's child) After four months of this a further gain in weight but no change in metabolism and a slight gain in pulse More vigorous roentgen-ray treatment was then started and with no other change there was a gradual improvement, with fall in pulse and metabolism which extended over a period of six months Two years later she was clinically much better but with a metabolism elevation of +25 per cent She reported again in December, 1921, in response to a letter The metabolism now was +15 per cent and she was clinically well The most interesting feature of this case is the prompt fall in metabolism and pulse coinciding with the resumption of roentgen-ray treatment

CASE 33—Mr B S, was a Jewish barber, aged 24 The last published note in his case is as follows "This case illustrates as well as any we have a

very toxic type of exophthalmic goiter, with steady improvement and ultimate complete recovery following essentially no therapy whatever beyond six roentgen-ray treatments" The events subsequent to the time this note was made (May 1919) are interesting

May 16, 1921, he reported of his own accord and said that for six months he had been feeling weak and rather dopey, though he had kept at his work. The clinical picture was the classical one of myxedema. The metabolism was — 20 per cent. He was started on thyroid, which quickly controlled the symptoms and brought the metabolism to a normal level. The progress and dosage of thyroid is shown in the chart. The last observation which shows a drop to — 15 per cent was after he had been off thyroid for about ten days because of his being in the Massachusetts Charitable Eye and Ear Infirmary for the removal of a small fibroid tumor of the vocal cord.

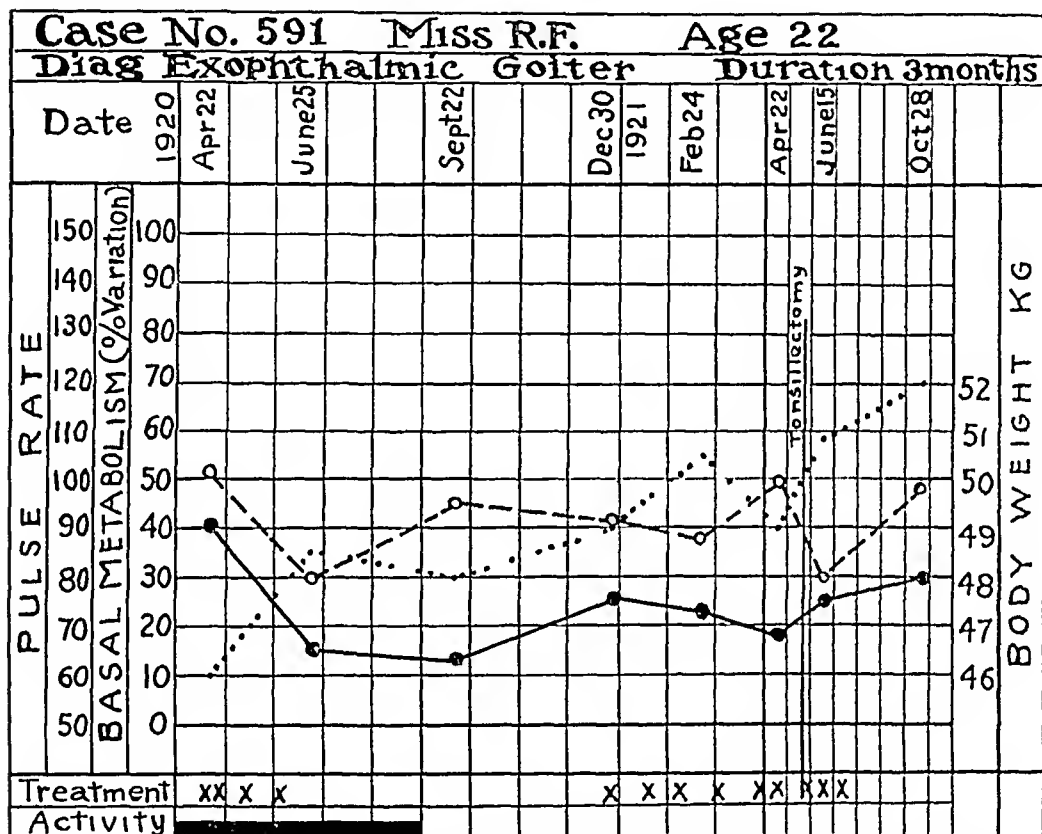


Fig 12—The solid line indicates basal metabolism, interrupted line, pulse rate, dotted line, body weight. Activity is shown by shading, solid black squares indicate rest in bed, half black squares, partial rest, white squares, usual mode of life.

## VI DISCUSSION

The objects we had in mind in undertaking this research were to find out whether roentgen-ray therapy in toxic goiter did any good or harm, and, if the former, whether it works in all cases, what the manner of its action is and whether the effect is permanent, also to discover if possible in what types of cases it worked best, provided any evidence was secured of its working at all

The data presented here, we believe, throw light on some of these problems. In the first place, in the recent series there were two out



of three patients with exophthalmic goiter who showed a noteworthy fall in pulse and metabolism coincident with exposure of their thyroid and thymus glands to the roentgen ray. This has led us to believe that in these cases the roentgen ray had a beneficial effect. Plummei<sup>38</sup> has objected to this conclusion on the basis that the natural course of exophthalmic goiter is a most uneven one and that improvements and relapses may occur at any time spontaneously. Therefore, he felt that our data proved nothing regarding the effect of the roentgen ray. He may be right. He remarked, and we deplore, the lack of control cases

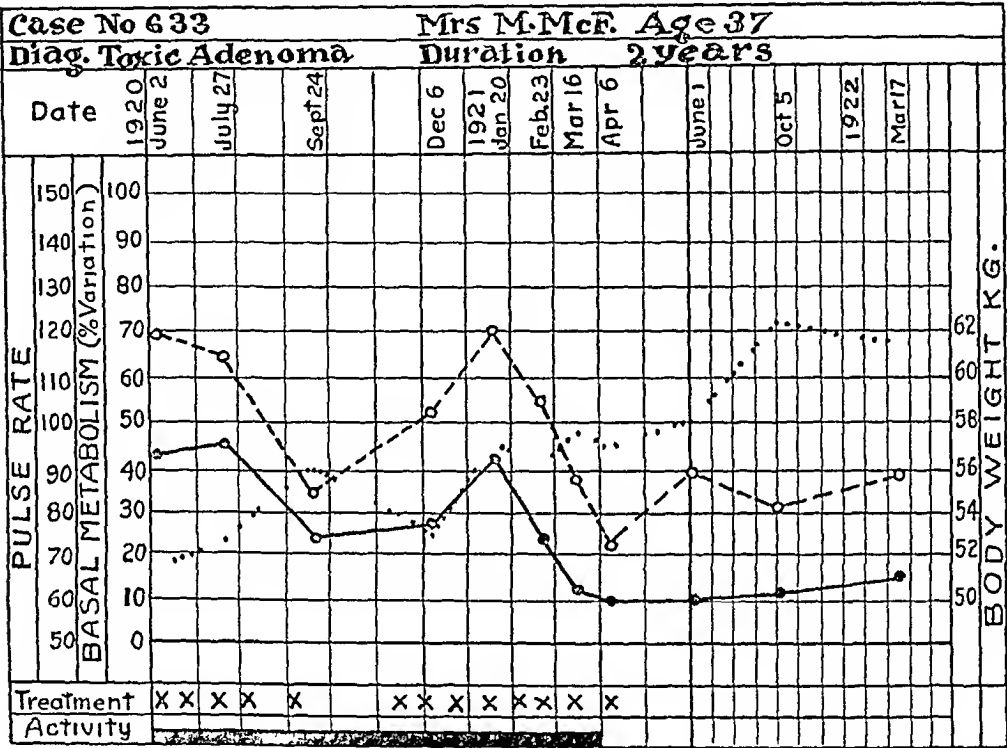


Fig 13—The solid line indicates basal metabolism, interrupted line, pulse rate, dotted line, body weight. Activity is shown by shading, solid black squares indicate rest in bed, half black squares, partial rest, white squares, usual mode of life

But until someone produces a satisfactory experimental exophthalmic goiter, controls will only be secured by chance. It is not permissible deliberately to withhold treatment from a group of patients with exophthalmic goiter for the sole purpose of accumulating scientific facts, nor would any but the very exceptional patient permit it should the attempt be made.

Until the study of exophthalmic goiter can be made experimentally, then, we shall have to get along without untreated controls, and glear

38 Plummer, H. S. In discussion of present paper when it was read in abstract before Association of American Physicians, May, 1922. Tr. Ass. Am. Phys., 1922.

what information we can by the methods open to us This difficulty applies to the study of many clinical problems It is by no means confined to exophthalmic goiter Does the dietetic treatment of peptic ulcer do any good? Nobody knows in Plummer's sense Patients with peptic ulcer get well with no treatment sometimes, just as exophthalmic goiter patients undoubtedly do in some instances

If we accept the theory that the symptoms manifested in hyperthyroidism are due to increased activity of the cells composing the thyroid

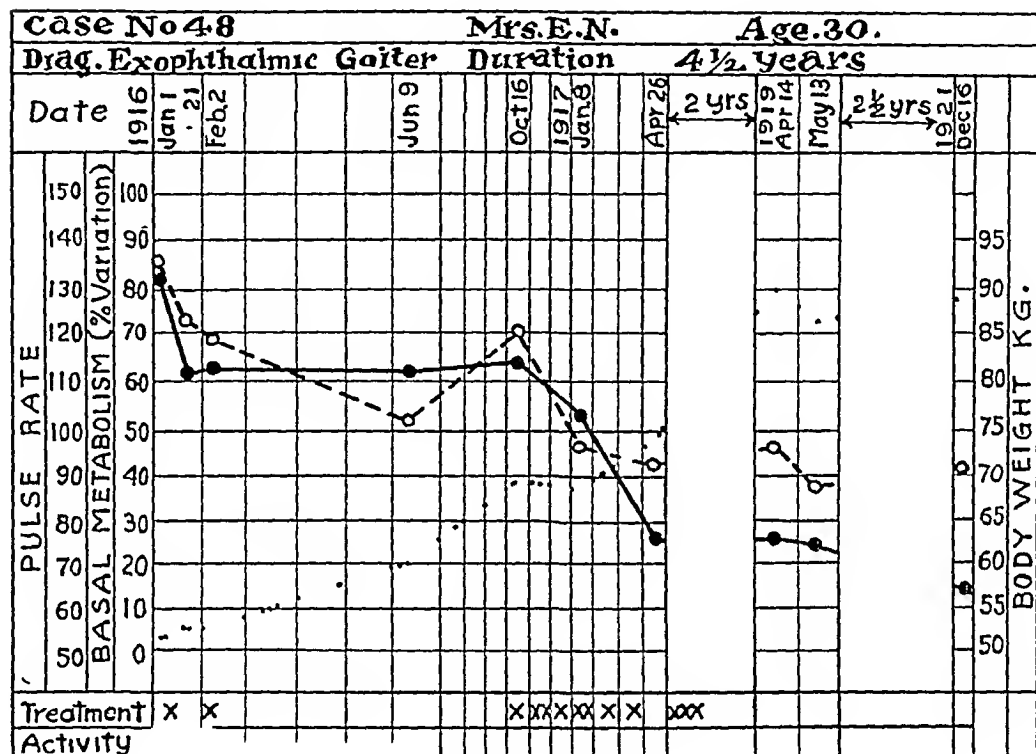


Fig 14—The solid line indicates basal metabolism, interrupted line, pulse rate, dotted line, body weight Activity is shown by shading, solid black squares indicate rest in bed, half black squares, partial rest, white squares, usual mode of life

gland, then the application of any method of treatment which is known to inhibit or destroy cell function would be rational

What, if any, evidence have we that in the roentgen ray we have such an agent?

It has been repeatedly shown by laboratory investigations that if a living organism be exposed to irradiation, retardation of growth, inhibition of function and death to the organism will take place, and that this change will be dependent on the amount of radiation absorbed, the character of the cells rayed, and the conditions to which they are subjected before and after irradiation

Schwartz<sup>39</sup> found that if he radiated dry vegetable seeds no variation whatever from the normal could be produced in the development of the plant. The cells of the germ in the dried state, with their metabolism reduced to a minimum, are not affected by irradiation. But, if through the addition of water the metabolism is stimulated and the seed germinates, it then becomes highly sensitive to radiation. This sensitiveness of the cell is in proportion to its metabolism. He also found that the sensitiveness of the plant diminishes with increase in age, and is slightly, if at all, affected at maturity. Similar experiments with lower forms of animal life have given similar results. From investigations of this kind and his own studies Bergonie was able to

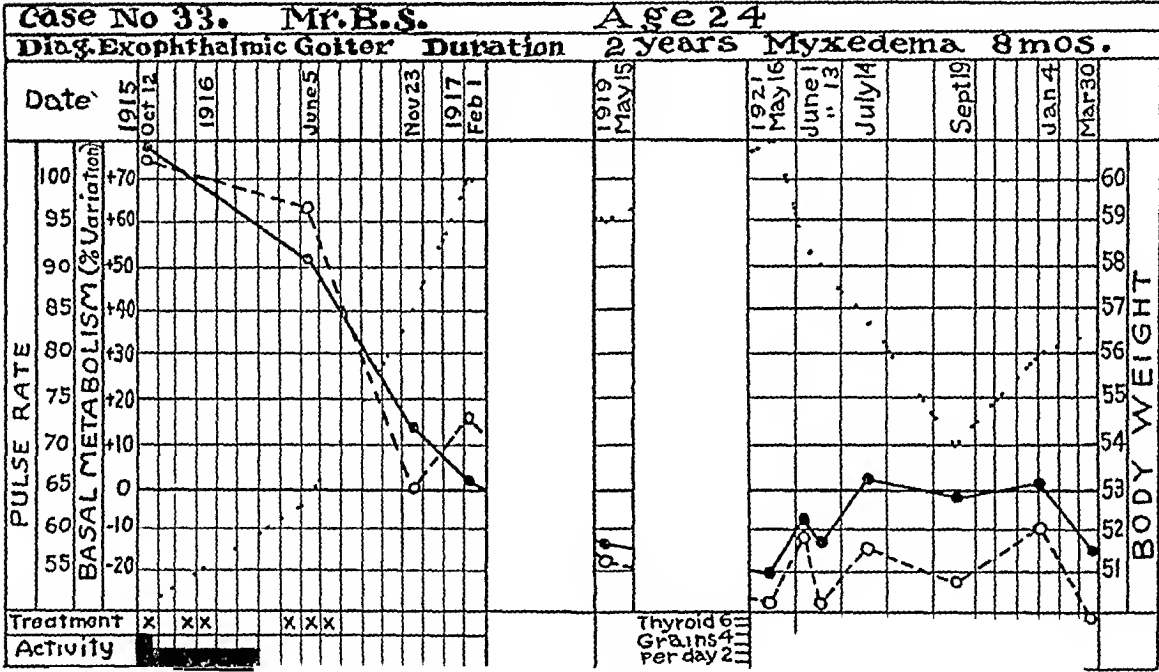


Fig 15—In the right hand portion the dose of thyroid given during the period of myxedema is shown by width of shading

formulate laws governing the sensitiveness of cells to radiation, and he states that the roentgen ray acts more intensively on the cell the greater its reproductive capacity, the longer its karyokinetic stage and the less its morphology and its function, except the power of reproduction, are definitely fixed. The first of these laws is by far the most important. All active cells are highly sensitive to radiation. Every cell of whatever kind it may be becomes less resistant to radiation as soon as it becomes active.

39 Schwartz Quoted by Wetterer, I, in Handbuch der Rontgen und Radium Therapie 1 373, 1919

In the field of clinical investigation, there is also abundant evidence that glandular function is especially sensitive to radiation. About one-fifth of the dose necessary to produce slight reddening of the skin if absorbed by the ovaries will cause cessation of the menstrual flow, and a similar dose to the testicles will cause the disappearance of the spermatozoa from the seminal fluid. A dose well below that, sufficient to cause injury to the skin, will stop the flow of saliva from the parotid gland. Slightly larger or repeated doses will cause any of these glands to become permanently atrophied. Furthermore, it has been observed that there is an increased sensitiveness in certain tissues in the young which lose their sensitiveness in the adult. Also, an increased sensitiveness may occur in tissues formerly less sensitive as soon as they begin to proliferate, as for example, the sensitiveness of the lacteal gland at the beginning of pregnancy compared with its low sensitiveness before conception, or at the height of its development.

From these observations, taken from many fields of investigation, it would seem that we have ample justification for supposing that the hyperactive thyroid would be favorably affected by radiation, and that this effect could be obtained with a dose well below that sufficient to cause injury to the overlying skin. It also becomes evident why the normal gland tolerates a much larger amount of radiation than the pathologically active one, and explains the failure to produce myxedema in animals except when using doses large enough to produce definite injuries to the glands and surrounding tissues.

From the clinical point of view we believe that data of the sort we have presented here are very highly suggestive, if not positive proof, of a beneficial effect of the roentgen ray in the majority of cases of exophthalmic goiter. It would be a very remarkable coincidence if we chanced to start roentgen-ray treatment in two out of three cases just as they were about to begin a rapid spontaneous drop. It is possible, but not probable. One can say positively, at any rate, that in two out of three of our cases there was improvement coincident with the inauguration of roentgen-ray treatment.

The rapidity of the drop is greater in the recent than in the prewar series. This very likely is due to incomplete dosage in certain cases of the earlier series, and sometimes to greater intervals between treatments.

If the roentgen ray has an effect, and if it fails to act in certain cases, the next problem becomes one of finding the type of case that will respond or fail to respond. With this in view we have made a survey of the severity, duration and age of the forty-four patients with

exophthalmic goiter who comprise our recent series. The average age, duration and metabolism (before treatment) of several subgroups is shown in Table 4.

This table would seem to indicate that neither the age of the patient nor the intensity of the hyperthyroidism as shown by the level of the metabolism is a factor in determining the success or lack of success of roentgen-ray treatment. The average length of the disease in the group that showed improvement was about seven months greater than that of the group that showed no improvement. It might be argued, therefore, that the former were more nearly at the point when spontaneous recovery might be expected to occur than the latter. The duration of exophthalmic goiter is given by different authors as from six months to several years. Cases running a spontaneously abortive course lasting but a few months may occur, but they are not the rule. It is also worthy of note that out of the twenty-eight improved cases there were eight in which the disease had lasted but six months or less.

TABLE 4—AVERAGES FOR EXOPHTHALMIC GOITER PATIENTS

Cases	Basal Metabolism			Duration of Disease Years			Age of Patient		
	Average	Maximum	Minimum	Average	Maximum	Minimum	Average	Maximum	Minimum
16 unimproved	52	85	21	1.4	3.0	0.2	36	62	22
28 improved	55	97	32	2.0	10.0	0.1	34	53	17
12 recovered*	51	85	32	2.0	5.0	0.5	33	53	17
7 relapsing*	61	97	37	1.5	8.0	0.1	30	44	17

\* Included in the group of 28 improved cases

at the time roentgen-ray treatment was started. In spite of the short duration of the disease, they all showed a definite drop with the roentgen ray, nor were they cases of a particularly mild type—the average metabolism of the group before treatment being +55 per cent and four months later +17 per cent. If the improvement following roentgen-ray treatment is not the result of the treatment but the mere natural course of the disease, one would expect to find certain cases getting progressively worse during treatment, but, as a matter of fact, we do not find such.

Another point which is strongly suggestive that the roentgen ray has a definite action on the thyroid is the development of myxedema. Two of our exophthalmic goiter patients, as has been reported elsewhere,<sup>31</sup> developed the classical picture of myxedema within the first four months of vigorous roentgen-ray treatment. Both were restored to normal levels by thyroid and in both thyroid was later discontinued without a return of the symptoms. Their thyroids were temporarily depressed apparently, not permanently as in spontaneous myxedema.

Another patient developed myxedema eighteen months after roentgen-ray treatment. This was a case of toxic adenoma. A fourth developed it five years after. It is more difficult to ascribe the effect in the last two cases to the roentgen ray, but the first two cases are highly suggestive.

While untreated control cases are lacking in this series, we have in a few cases a control period. That is to say, metabolism observations were secured over a considerable period before roentgen-ray treatment was started. This occurred in Cases 48, 456, 628 and 909. In each of these, directly coincident with roentgen-ray treatment, there was a rapid improvement, although they had been stationary before, and with the addition of no new factor but the roentgen ray. This evidence, too, we believe suggests strongly that the roentgen ray has an effect.

The results of treatment of exophthalmic goiter as we see them now are in brief these. In about two thirds of the cases the inauguration of vigorous roentgen-ray treatment is followed by a progressive improvement, as shown by clinical signs and by the behavior of pulse, metabolism and body weight. This continues for from four to five months, during which time about five suberythema doses of roentgen ray are given to the thyroid and thymus. This improvement may go to the extent of recovery or may fall short of that. When the latter, continuation of the roentgen-ray treatment seems to be of but little value. On the other hand, certain cases that show a marked improvement may later, after the cessation of roentgen-ray treatment, have a return of the hyperthyroidism, in these cases a second course of treatment not infrequently is accompanied by a second rapid improvement.

In other words, the data presented here indicate that the beneficial effect of roentgen ray, if there is to be any such, should be obvious during the first four or five months of treatment. It would seem therefore that the roentgen ray is a useful therapeutic agent in the management of exophthalmic goiter, but it is by no means an ideal one. Patients who do not respond to the roentgen ray in 4 or 5 months, and those who, although improved, still remain somewhat thyrotoxic at the end of that time, should be given the benefit of surgery. Our conception of the proper way of using the roentgen ray in exophthalmic goiter is that in most cases it should be given a trial with the idea that it may effect a cure, or if not, that it may, through reducing the degree of hyperthyroidism, make the patient a better operative risk.

Of course, it may be asked why, if the roentgen ray has no effect in certain cases, should it be used in any case? Why should not all patients be subjected to operation at once? The obvious answer to this is that in spite of the remarkable success of modern operative procedures in the hands of specially skilled surgeons, there still remains

a definite mortality This mortality, we believe, can be reduced or abolished by not resorting to surgery at once in every case, but by making use of the roentgen ray first, partly because we believe that by such a program some patients may never need operation, while others will be in better shape to stand it at a later date because of their previous irradiation

Neither roentgen ray nor thyroidectomy is an ideal method of treatment, for neither in all probability attacks the cause of the disease The cause of exophthalmic goiter is entirely unknown, but it is probable that it does not originate within the thyroid Nevertheless, the resulting phenomena in the patient, and the ones from which he needs to be protected, are directly due to the overactivity of that gland Until the cause of the disease is known, therefore, and some agent found which can directly combat that cause, it is reasonable to continue to attack the thyroid The surgeon seeks to do this by the removal of a portion of the gland The radiologist tries to destroy some of the tissue *in situ* The object is the same, the agent used differs Neither agent is entirely satisfactory, each may be used to supplement the other

In the past we have sometimes persisted with the roentgen ray over long periods and given large numbers of treatments, although the patient showed little or no improvement In view of such experience, we now feel very definitely that this is an undesirable thing to do The roentgen ray in time seems to lose whatever effect it may have on the thyroid, just as it does ultimately on the leukemic spleen When it ceases to produce improvement in exophthalmic goiter, it should, in our opinion, be abandoned and thyroidectomy substituted in those cases in which a thyrotoxicosis persists Every patient with exophthalmic goiter should be made the subject of individual study, and the various therapeutic measures at our disposal should be used alone or combined as that particular case may demand

In the matter of toxic adenoma, the problem is altogether different In that disease the cause appears really to lie within the thyroid, in the adenoma *in fact*<sup>40</sup> The surgical removal of the tumor cures the disease There would seem, therefore, not to be the same desirability for preliminary roentgen-ray treatment We have used the roentgen ray, therefore, in this disease only with patients who have refused operation Nevertheless, it is interesting to note that they, like those with exophthalmos, show improvement In fact, all fourteen of our cases so treated improved In four cases the improvement was slight In five it was marked, and in five there was a cessation of all signs and symptoms

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<sup>40</sup> Plummer, H S Interrelationship of Function of the Thyroid Gland and of Its Active Agent Thyroxin in the Tissues of the Body, *J A M A* 77 243 (July 23) 1921

of thyrotoxicosis In six cases the goiter disappeared during the treatment The fact that cases of toxic adenoma improve while under roentgen-ray treatment, as well as cases of exophthalmic goiter, is, we believe, strong evidence that the effect is really the result of the irradiation, for the course of toxic adenoma untreated is continuous One does not expect spontaneous remission of the sort found in exophthalmic goiter

It has been our object ever since this research was started to follow our patients for a long period of time We have been fortunate in being able, in a number of instances, to secure data extending over a period of several years In dealing with a disease like either of the varieties of toxic goiter, the real benefits of treatment can only be evaluated properly by studying the late results It was with this ideal in mind that we have introduced in the present paper recent data in cases previously published The larger series of the last three years which has formed the basis of the above discussion will serve well to illustrate the immediate results of roentgen-ray treatment, but the smaller prewar series will show the results from five to seven years after treatment Seven out of fifteen patients in that group treated solely by the roentgen ray in whom there was originally apparent recovery, have remained well Crile has said that the roentgen ray does not control exophthalmic goiter, that it may produce great benefit but with recrudescence, as a rule<sup>41</sup> This has not been our experience Recrudescence may occur, but it is not by any means the rule

*Effect of Rest*—In ascribing improvements in any disease to a certain therapeutic agent it is always easy to overlook the factor of rest This is particularly true of exophthalmic goiter There is no question that complete rest alone is often accompanied by a decrease in the degree of hyperthyroidism We have indicated in our charts and tables to what extent rest may have been a factor in the cases under discussion It seems to us that it is a minor one Not a few patients showed the characteristic improvement with no rest at all

*Focal Infection*—The matter of focal infection has been given consideration in our clinic We have made it a practice to remove obvious foci, infected tonsils and the like, but cannot say that we have seen any startling effects from such procedures Observations before and after tonsillectomy will be found in four of the cases given in Tables 1 and 2 (Cases 338, 591, 603 and 866) We feel that in the management of toxic goiter the correction of infectious foci is impor-

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41 Crile, G W Discussion, Symposium on Basal Metabolism in Clinical Medicine, J A M A 77 355 (July 30) 1921



tant, but we have not seen any reason to believe, as McCarrison<sup>42</sup> does, that they are an important factor in the production of the disease. They may serve to aggravate or prolong the thyrotoxicosis.

*Pregnancy*—In four cases of exophthalmic goiter we have secured observations before and during pregnancy, and in one case after pregnancy as well. Mrs. A. B. (Case 374) showed a marked improvement with a combination of roentgen-ray therapy and ligation of vessels. She married June 4, 1921, November 16 her metabolism was + 16 per cent, April 18, 1922, when six months pregnant, it was + 13 per cent. She has had no return of her symptoms of hyperthyroidism. Mrs. J. L. (Case 485) developed myxedema during roentgen-ray treatment. When last seen she was four months pregnant, with no return of symptoms of hyperthyroidism or hypothyroidism. Another woman (Case 762) had failed to respond to the roentgen ray. Later a hemithyroidectomy was done which was followed by some improvement. A definite increase in her thyrotoxicosis manifested itself when she became pregnant, but when three months pregnant a further thyroidectomy was done without interruption of her pregnancy, and when last seen, her metabolism was normal and her symptoms of hyperthyroidism had disappeared. Mrs. F. S. (Case 802) who after recovery following roentgen-ray treatment went through a pregnancy without recurrence, has been referred to earlier.

*Cardiac Complications*—Our studies of the cardiac complications have not been as complete as we hope to have them in the future. Ordinary examinations of the heart have been made from time to time, and in the fibrillating cases electrocardiograms have been taken. We have not, however, carried out any of the newer functional tests of the heart. Our clinical observations have not disclosed any evidence that patients received added cardiac damage because they were treated by the roentgen ray instead of immediate operation. We recognize the need of further study on this problem and propose to make it

## VII CONCLUSIONS

1. We believe that the data presented here show that the roentgen ray probably has a beneficial effect in toxic goiters, and that for that reason it has its place in our armamentarium for treating these diseases.

2. About two-thirds of the patients with exophthalmic goiter so treated show either recovery or improvement coincident with the treatment. The remaining third neither improve nor grow worse.

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<sup>42</sup> McCarrison, R. *The Thyroid Gland in Health and Disease*, New York, William Wood & Co., 1918.

3 In exophthalmic goiter, when treated by the roentgen ray, if good results are not secured in a few months, surgery should be employed. Prolonged roentgen-ray treatment in patients showing no response is undesirable. This is a fact which has been impressed on us particularly in our recent work. We have not emphasized it before, and therefore, do so now.

4 Some patients with exophthalmic goiter who are not cured by the roentgen ray are, perhaps, made better operative risks by it. A combination of the two forms of treatment may sometimes accomplish more than either does alone.

5 In toxic adenoma there seems to be a similar improvement to that noted in exophthalmic goiter, but so far we have used it only with patients who have refused operation. In toxic adenoma, in contrast to exophthalmic goiter, surgery probably removes the actual cause of the disease, the adenoma. The indication for surgery would, therefore, seem more definite than in exophthalmic goiter. Even in toxic adenoma, however, in certain cases that are too thyrotoxic for safe operation, the roentgen ray may be used to advantage.

6 To make a proper use of the roentgen ray in the management of toxic goiter of either variety, its limitations should be recognized and it should be intelligently correlated with other therapeutic measures as the individual case may demand.<sup>43</sup>

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<sup>43</sup> Since going to press, an interesting article by Drs. Kessel, Lieb and Hyman (*J. A. M. A.* 79:1213 [Oct. 7] 1922) has come to our attention. They are supplying data on patients treated by rest alone, which will be of great value in settling some of the disputed matters regarding thyrotoxicosis.

# THE CORRELATION OF VITAL CAPACITY WITH STEM HEIGHT<sup>\*</sup>

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The vital capacities of normal men vary with their sizes. The measurement of size which furnishes the best standard for estimating the normal vital capacity is, however, still under discussion. In a recent study of male students at Stanford University,<sup>1</sup> a comparison was made between vital capacity, on the one hand, and the height, the weight, and certain combinations of height and weight on the other. The stem heights of these students were not measured, and since Dreyer places the highest value on stem height in estimating the normal vital capacity, the present study was undertaken for the purpose of comparing stem height with standing height as a vital capacity standard for normal young men.

## SUMMARY OF PRESENT DATA (STANFORD 2) COMPARED WITH PREVIOUS STANFORD DATA AND WITH A COMBINATION OF STANFORD, HARVARD AND OXFORD DATA

	Stanford (2)	Stanford (1)	Stanford, Harvard and Oxford
Number	400	400	1,444
Means			
Height	175.9	175.9	176.2
Stem	91.5		
Vital capacity	4,421	4,616	4,426
Standard Deviations			
Height	6.48	7.121	6.805
Stem	3.30		
Vital capacity	595.7	655.8	646.9
Coefficients of Correlation			
Height Vital capacity	0.46	0.55	0.53
Stem Vital capacity	0.47		
Height Stem	0.73		

Observations were made on 400 male students at Stanford University, whose ages ranged between 18 and 30 years. The standing heights were measured in bare feet and the stem heights were measured according to the method described and illustrated by Dreyer.<sup>2</sup> Each student was shown how to use the spirometer and was then given three trials, the maximum reading being recorded as his vital capacity.

The accompanying chart shows the average vital capacities for the different stem height groups. Two lines have been added to this figure

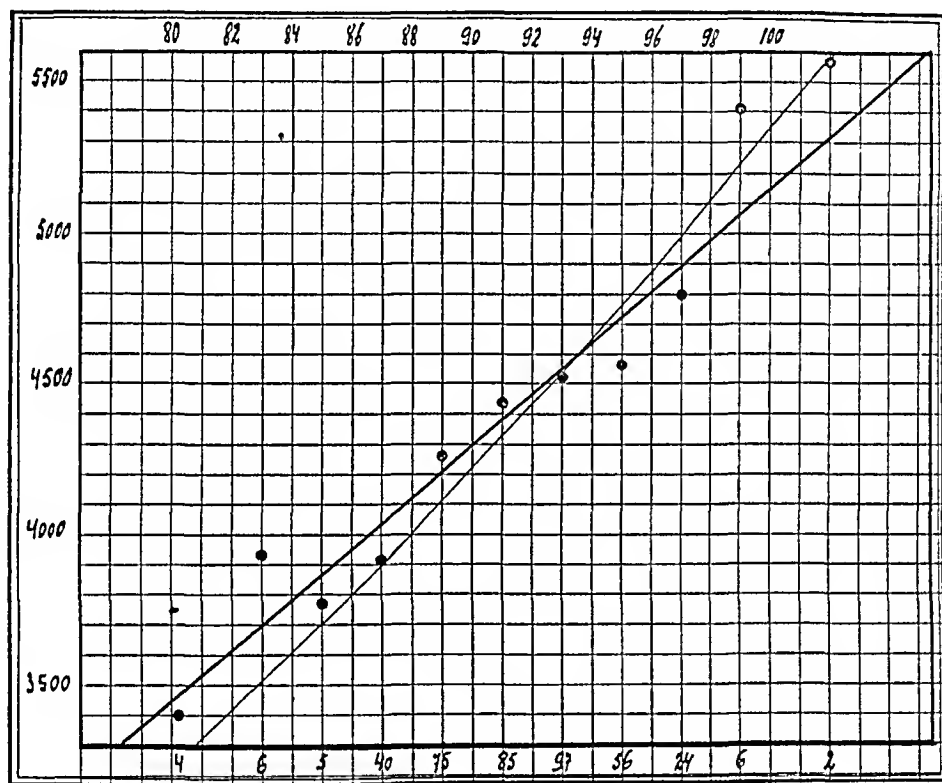
<sup>\*</sup> From the Department of Medicine, Stanford University.

1 Hewlett, A. W., and Jackson, N. R. The Vital Capacity in a Group of College Students, *Arch Int Med* 29:515 (May) 1922.

2 Dreyer, G. The Assessment of Physical Fitness, New York, Paul B. Hoeber, 1921.

The heavier line represents the linear relation between vital capacity and stem height as calculated from the present data, the lighter line represents the relation given by Dreyer for "Class A" individuals. It will be noted that the slope of Dreyer's line differs somewhat from that which best fits our data, and that, furthermore, for the range of stem heights under consideration, the curve in Dreyer's line is not marked. We see no reason for adopting Dreyer's complex formula, at least for adult men, when a linear formula will answer the same purpose.

The linear relationships between vital capacity on the one hand, and standing height or stem height on the other, can be calculated and



The ordinates represent vital capacities and the abscissas stem heights. The dots represent the average vital capacities for the different stem-height groups, the number of observations in each group being given below. The straight heavier line has been calculated to fit our data. The lighter curved line represents that given by Dreyer for "Class A" individuals.

expressed mathematically by the methods commonly used in statistical studies<sup>1</sup>. The more nearly the coefficient of correlation approaches unity, the closer is the relation between two sets of data obtained from the same group of individuals.

The accompanying table shows the means, the standard deviations and the coefficients of correlation for the present set of observations, together with some corresponding figures taken from the previous paper. It will be observed that the coefficient of correlation between

standing height and vital capacity was 0.46 and that the coefficient of correlation between stem height and vital capacity was 0.47. This difference is not significant.

#### CONCLUSION

In a group of male college students the correlation between stem height (Dreyer) and vital capacity was not significantly better than the correlation between standing height and vital capacity.

# A CLINICAL REPORT ON THE USE OF QUINIDIN SULPHATE \*

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AND  
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BOSTON

## INTRODUCTION AND HISTORICAL RESUME

Although eight years have passed since Wenckebach<sup>1</sup> noted the restoration of normal rhythm by quinin in cases of auricular fibrillation, there is but little agreement regarding the indications and limitations for the use of this drug or its more effective isomer, quinidin. As Wenckebach found quinin but rarely effective, it was used but little for the four years following his report. Then, in 1918, Frey, testing other alkaloids obtained from cinchona in cases of auricular fibrillation, showed the greater efficacy of quinidin in restoring normal mechanism, and gave the investigation new impetus. This first report,<sup>2</sup> embodying the results obtained in his first twelve cases, was followed by another report on twenty-two cases.<sup>3</sup> Here he outlined the method of administration still used with little change, and noted the advisability of previous digitalization and test dosage with quinidin. His observations on recurrence, toxic and untoward results, and changes in pulse rate have been added to but little since that date. From 1918 to the present date a large number of investigators have reported their observations, usually on small series of cases of auricular fibrillation, which have not permitted very satisfactory conclusions. In 1921, Frey<sup>4</sup> again reported his cases, then fifty in number, confirming his previous observations and commenting on the relation of the duration of the arrhythmia to the results obtained from use of the drug. Boden and Neukirch<sup>5</sup> and others have reported favorable results from use of the drug in paroxysmal tachycardia and premature beats. Later Lewis, Drury, Ilescu and Wedd<sup>6</sup> reported their observations on the mode of action of

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\* From the Massachusetts General Hospital, Boston, and the New Haven Hospital, New Haven, Conn.

\* Read in part at the annual meeting of the American Society for Clinical Investigation, Washington, D C, May 1, 1922.

1 Wenckebach, K F. *Die unregelmässige Herzthätigkeit*, 1914.

2 Frey, W. *Berl klin Wchnschr* **55** 450 (May) 1918.

3 Frey, W. *Berl klin Wchnschr* **55** 849, 1918.

4 Frey, W. *Deutsch Arch f klin Med* **136** 70 (April) 1921.

5 Boden, E, and Neukirch, P. *Deutsch Arch f klin Med* **136** 181, 1921.

6 Lewis, T, Drury, A N, Ilescu, C C, and Wedd, A M. *Brit M J* **2** 514 (Oct) 1921.

quinidin with relation to the circus movement of auricular fibrillation and flutter and so placed the use of the drug upon a rational basis

During this period of investigation, a number of writers have noted serious untoward results under quinidin Benjamin and Von Kapff,<sup>7</sup> Ellis and Clarke-Kennedy,<sup>8</sup> Eyster and Fahr,<sup>9</sup> Haass,<sup>10</sup> Sappington,<sup>11</sup> Wilson and Hermann,<sup>12</sup> Hewlett and Sweeney,<sup>13</sup> Frey and others As these included cases with fatal and nonfatal embolism, increased failure and unexplained sudden death, the profession has questioned the utility of a drug producing such effects That by its use excellent results obtain in certain cases, many, perhaps most, writers have agreed, and remembering the one hundred years of neglect digitalis suffered<sup>14</sup> following the classical work of Withering in 1785 (and this in an age more open to drug therapy than our own), we hesitate to discard without due trial a drug so potent as quinidin If it were possible to choose for its use only those cases likely to yield favorable effects and to avoid the cases likely to suffer untoward results, it would seem a valuable therapeutic agent

During the last year at the Massachusetts General Hospital and the New Haven Hospital a series of cases of the nonparoxysmal ("permanent") type of auricular fibrillation and flutter have been treated with quinidin This report deals principally with this type of case In addition a small series of the paroxysmal type of fibrillation and flutter and a few cases showing premature beats or heart block have been observed under the influence of the drug An attempt has been made to correlate the observations made with those found in the literature A preliminary report of the present study was published last year<sup>15</sup>

#### CASES OF NONPAROXYSMAL AURICULAR FIBRILLATION AND FLUTTER

At the Massachusetts General Hospital and the New Haven Hospital, seventy-one cases of nonparoxysmal ("permanent" or "chronic") auricular fibrillation and four cases of nonparoxysmal flutter have been treated with quinidin sulphate,—a total of seventy-five cases The first

7 Benjamin and Von Kapff *Deutsch med Wchnschr* **47** 10, 1921

8 Ellis and Clarke-Kennedy *Lancet* **2** 894, 1921

9 Eyster, J A E, and Fahr, G E *Quinidin in Auricular Fibrillation*, *Arch Int Med* **29** 59 (Jan) 1922

10 Haass, H *Berl klin Wchnschr* **58** 540, 1921

11 Sappington, S W *Quinidin Treatment of Auricular Fibrillation* *J A M A* **78** 59 (Jan 7) 1922

12 Wilson, F N, and Herrmann, G R *Cerebral Embolism Following Arrest of Auricular Fibrillation by Quinidin*, *J A M A* **78** 865 (March 25) 1922

13 Hewlett, A W, and Sweeney, J P *Quinidin Treatment of Auricular Fibrillation*, *J A M A* **77** 1793 (Dec 3) 1921

14 Pratt, J H *Digitalis Therapy*, *J A M A* **71** 618 (Aug 24) 1918

15 White, Marvin and Burwell *Boston M & S J* **185** 647, 1921

sixty cases were practically unselected, the majority of the remaining fifteen cases were selected on the basis noted below. In nearly all the cases showing congestive failure, digitalis was administered before the use of quinidin was begun. All patients were given 0.2 gm twice (a two hour interval) the day preceding the full dosage as test doses for sensitivity to the drug. After that the usual method of administration was 0.4 gm five times daily by mouth in capsule or tablet form at two hour intervals, in some cases increasing to 0.6 or 0.8 gm five times daily. Usually the drug was continued until restoration of normal rhythm or development of significant toxic symptoms. Each case was

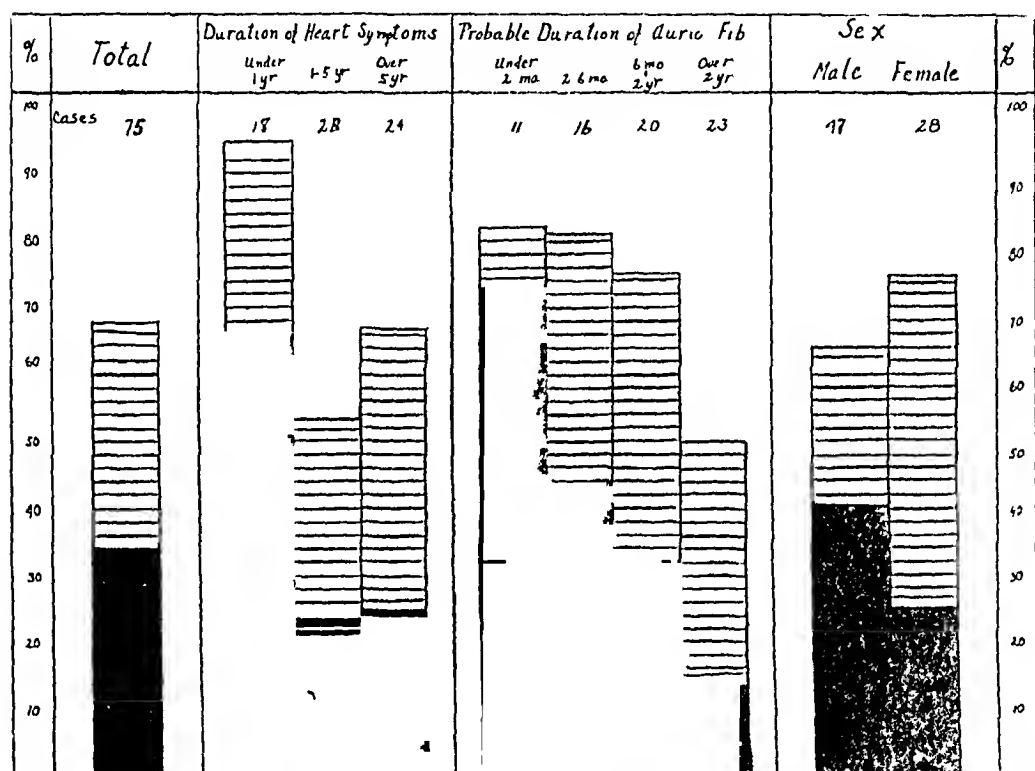


Fig 1—Relation of various factors to restoration and maintenance of normal rhythm. Abscissas represent the groups of cases under consideration, ordinates the percentage responding to quinidin. The column represents the percentage of a given group restored to normal rhythm, the shaded part those relapsing, the black part those still maintaining normal mechanism. Above each column is noted the number of cases in that group.

studied carefully by the usual laboratory and clinical methods and by electrocardiograms at least once daily. Seven of the patients were handled as outpatients, all the others remaining in the hospital during the period of quinidin administration.

**Total Series**—Of the total series of seventy-five cases, fifty-one cases, or 68 per cent, were restored to normal rhythm by quinidin, twenty-six cases, or 34 per cent, still maintain it after intervals varying from a few days in the last case to more than ten months (Case 6).



In other words, in a largely unselected series of cases two-thirds were restored to normal rhythm and one-third maintain it (Fig 1).

*Sex*—Though a higher percentage of females than males were restored to normal rhythm, a lower percentage maintained it (Fig 1) Sex cannot be considered an important factor in determining restoration or relapse

*Age*—Consideration of the age of the patient (in groups of ten year periods) with relation to the restoration and maintenance of normal mechanism showed that while patients more than 50 years of age presented a higher percentage of restoration than those between 30 and 50, the percentage of maintenance was strikingly equal The low percentage in the first group (ages from 20 to 29) may have been the result of the small number of cases in that group There was, then, no marked parallelism between age and response to quinidin (Fig 2)

*Etiologic Type of Heart Disease*—Four cases of the series were of doubtful etiology The remaining seventy-one cases were divisible into four groups rheumatic, arteriosclerotic, thyroid, and thyroid plus rheumatic The last two groups, containing only three cases each, were too small to permit drawing conclusions as to their relative response to quinidin The arteriosclerotics had a higher percentage of restoration (76 per cent) than the rheumatics (61 per cent), and a higher percentage of maintenance (43 per cent as compared to 27 per cent for the rheumatic) (Fig 2) Since the arteriosclerotic group comprises largely the older patients, these observations correspond roughly to the variations with age as noted above That this difference in response may be due to a factor other than the etiologic type will be considered later in this communication under the discussion of the variation in response with respect to congestive failure

*Duration of Heart Signs or Symptoms*—The actual duration of the cardiac disease being difficult to estimate, the duration of heart symptoms or recognized signs was considered for its possible relation to response to quinidin (Fig 1), dividing the cases into three groups and excluding five cases in which the duration was questionable

The cases in the group of from one to five years' duration had a reasonably equal percentage of maintenance of normal rhythm (21 per cent) with the cases of more than five years' duration (25 per cent), the latter of the two groups had a slightly higher percentage of restoration (66 per cent as compared with 53 per cent for the group of cases of shorter duration) The group of eighteen patients whose cardiac symptoms were of less than one year's duration had high percentages of restoration (94 per cent) and maintenance (66 per cent) These differences will be referred to again in the discussion of the relation of duration of fibrillation to response to quinidin

*Probable Duration of Fibrillation*—In all of the cases, except five, it was considered possible, by careful history taking, use of outpatient records or reports from the patient's previous physician to approximate the probable duration of fibrillation or flutter. Grouping the remaining seventy cases according to this duration, a striking parallelism appeared both to restoration and maintenance of normal rhythm (Fig 1). Of the group of eleven cases with fibrillation of less than two months' duration, 82 per cent were restored to sinus rhythm and 73 per cent maintain it. Of the cases, twenty-three in number, with a fibrillation more than two years old only 48 per cent were restored and but 13 per cent maintained normal mechanism. Duration of fibrillation seems to be the most important factor determining response to quinidin.

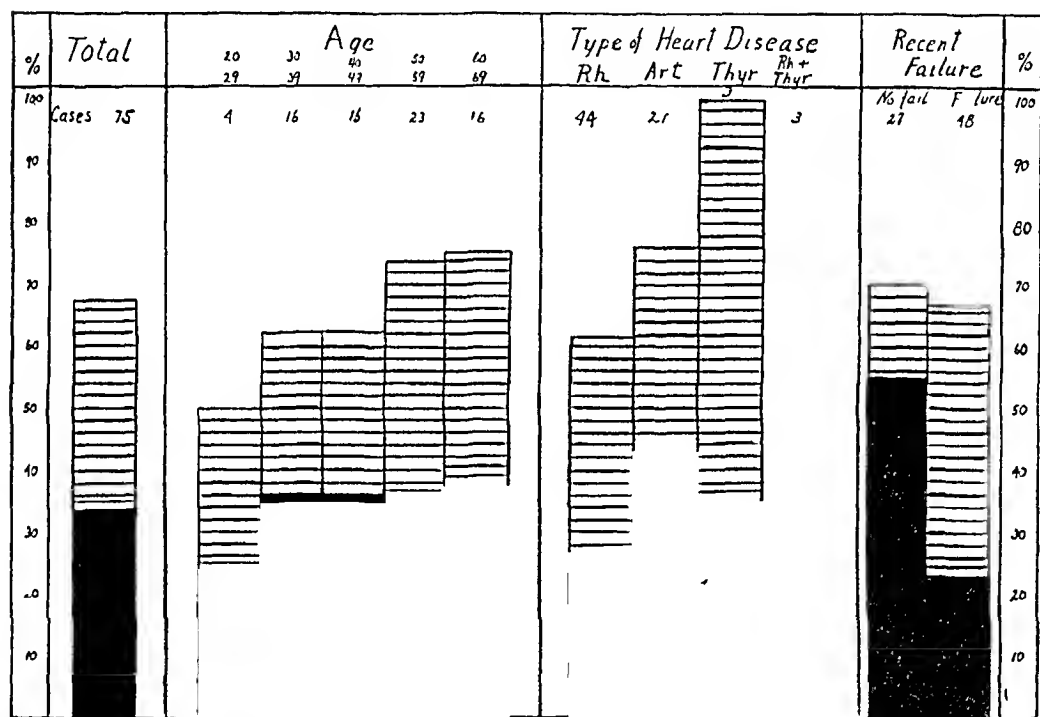


Fig 2—Similar to Figure 1

In discussing the variation in response with relation to duration of heart symptoms (Fig 1) a higher percentage of favorable results was noted in the first group, of the eighteen cases in this group only three had fibrillation of more than six months' duration, and it is probable that the latter factor was the one responsible for the response in that group. Similarly, the slightly better results in the third group than the second group may be explained by the fact that of the second group only 19 per cent had fibrillation of less than six months' duration, while 27 per cent of the third group had fibrillation of such short duration.

*Failure of the Congestive Type*—While those cases showing objective congestive failure (edema, enlarged liver, pulmonary edema, etc.)

on admission were restored to normal mechanism in about an equal percentage to those not showing such failure, the percentage of maintenance in the former was less than half that in the latter (Fig 2). A similar tabulation of cases showing such failure at the beginning of quinidin administration (after digitalization) yielded similar results. Though cases with failure may be restored as readily as the others they present a much greater tendency to relapse.

In the consideration of the relative response of the rheumatic and arteriosclerotic types, it was noted that the latter responded more frequently than the former, this difference may have been due, in part at least, to the greater frequency of congestive failure in the cases of the rheumatic group (72 per cent) than in the arteriosclerotic group (57 per cent).

Cases with a history of periods of failure in the past seemed to respond poorly to quinidin whether or not there was marked failure at the time of quinidin treatment.

It was of interest to note that congestive failure was about equally frequent in the groups of patients with auricular fibrillation of short duration and in those of long duration.

Congestive failure (objective), the expression of myocardial failure appears to be the second of the two important factors determining response to quinidin. Presumably, the weakened cardiac muscle is in some way more resistant to the influence of quinidin than the normal or less damaged muscle.

*Digitalization with Relation to Response to Quinidin*—As only five patients of the series had not received digitalis prior to quinidin, it was not possible to determine comparative response between digitalized and nondigitalized cases. However, the fact that congestive failure was unfavorable for the production of maintained normal mechanism suggested that, in cases with such failure, digitalis probably favored rather than antagonized the action of quinidin. In a large number of cases heavy digitalis dosage was given just prior to quinidin and yet normal rhythm appeared, often with the smallest doses of quinidin. All the cases, except two, in which restoration of normal rhythm was not obtained or was transient, apparently reacted quite as well to digitalis as before the use of quinidin. The two exceptions, in which a "fixed flutter" was produced by quinidin will be described later. From these observations it appeared not only that there was little or no antagonism between the two drugs but also that digitalis was distinctly indicated in cases with failure before the initiation of quinidin.

*Quinidin Dosage*—In the cases restored to normal rhythm, the total dosage varied from 0.4 gm (the test doses only) in two cases to 23.2 gm, the period of administration from one-half day to ten and one-half

days, the daily dose from 16 gm to 4 gm and the single dose from 02 gm to 08 gm. Of the fifty-one cases restored, 86 per cent required less than 9 gm total dosage. There was no close correspondence between the duration of fibrillation and the dosage required to restore normal rhythm (Fig 3). There was essentially no greater tendency to relapse in the cases requiring large dosage than in the cases in which small doses were sufficient. Some of the cases requiring the largest dosage have given the most satisfactory clinical results. In the reported cases of untoward results under quinidin, the dosage has usually been small. While the present lack of exact knowledge of the drug inclines one to keep the total dosage within the limits under which

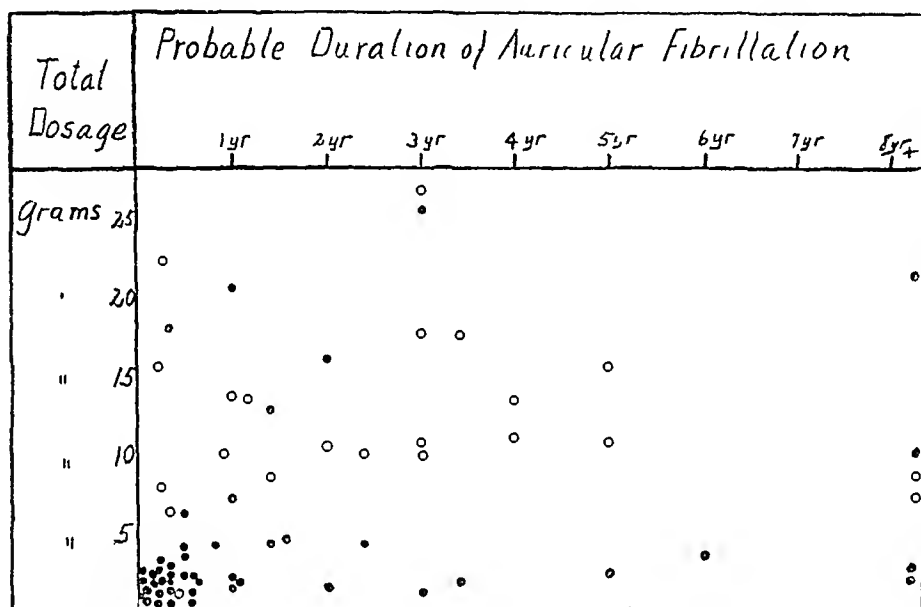


Fig 3—*Relation of dosage to probable duration of fibrillation* The black dots represent those cases restored to normal rhythm, the circles those cases not restored. Abscissas=duration of fibrillation, ordmates=dosage of quinidin given.

the majority of patients react, observations to date have presented no contraindications to the use of the large doses, and it may be that in a favorable case under close observation the drug should be continued until normal rhythm is established or toxic symptoms develop

Thirteen patients either failing to respond to the first course or relapsing immediately were given subsequent courses. Only two of those restored by such additional courses still maintain normal mechanism. When a patient fails to respond to an adequate first course or relapses quickly, further quimidin is usually not worth while.

After restoration of normal rhythm, twenty-four of the fifty-one patients (usually alternate cases) were given rations of quinidin in varying doses over varying periods. About an equal percentage

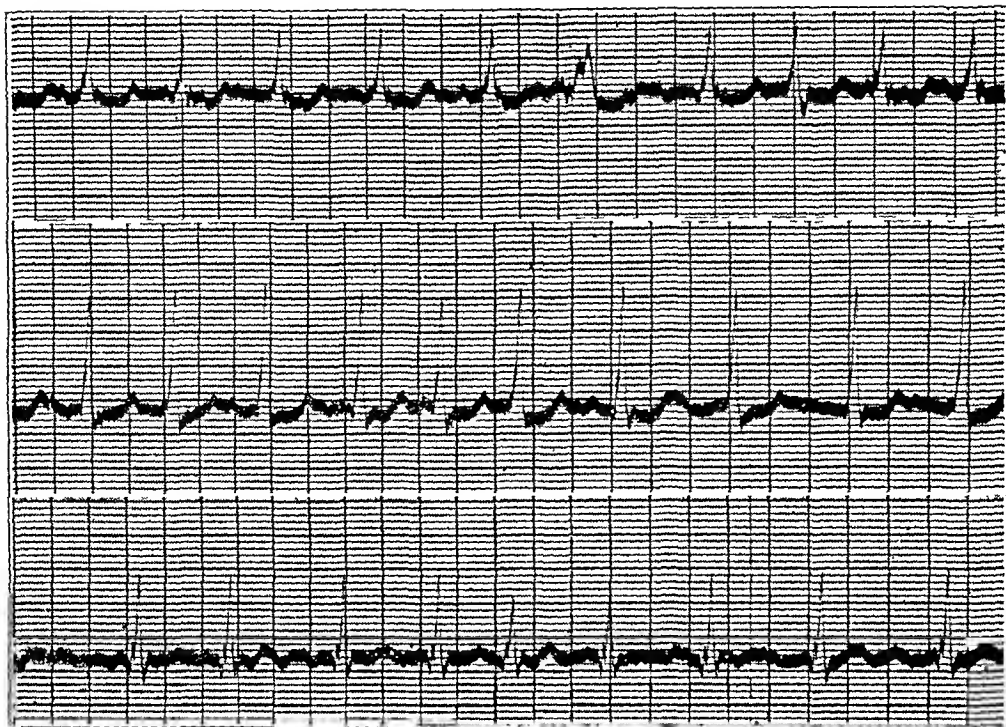


Fig 4—Electrocardiogram of R M Auricular fibrillation (before quimidin), Leads I, II and III



Fig 5—Auricular fibrillation Bundle branch block

relapsed in those rationed and those not rationed. As the cases rationed were generally more favorable for relapse (a higher percentage of cases with fibrillation of long duration) than those not so treated, the rationing did not prove so ineffective as the figures suggest. In addition, the dosage given in the earlier cases later proved to have been entirely inadequate. Patients with fibrillation of short duration and no failure need less rationing after reestablishment of sinus rhythm and possibly in some cases none at all. One patient reported four months after restoration with paroxysms of fibrillation that have been entirely prevented to date by rations of 0.4 gm daily. At New Haven, Marvin gave routine rations of 0.4 gm three times daily the first two days after restoration, twice daily the succeeding two days, once daily the next two days and then once weekly and considered this method to be usually effective. At the Massachusetts General Hospital as high as 0.4 gm daily over periods of from several weeks to months have been given in some cases with no apparent ill effects. Only further study will determine whether such long continued dosage bears hidden ill effects.

*Changes in Cardiac Mechanism*—A number of interesting changes in the cardiac mechanism appeared during quinidin administration. Even without direct chest leads, many cases demonstrated definite slowing of the auricular circus rate before or without restoration of sinus rhythm. Auricular flutter was observed in seventeen cases, of these, eleven later attained normal rhythm, two remained "fixed" in flutter despite digitalis and additional quinidin and four reverted to fibrillation. Under quinidin transient bundle branch block occurred in two cases, one during the transition to normal rhythm, the other without restoration of sinus mechanism (Figs 4 and 5). The first of these cases presented at the same time a regular tachycardia without evident *P* waves. Four other cases showed transient intraventricular block of lesser degree (aberration type) (Fig 6), all but one during the period of transition to normal rhythm. One other case for some hours before the appearance of normal rhythm showed a regular slow rhythm with no evident *P* waves.

In fourteen cases the *PR* interval after restoration of sinus rhythm exceeded 0.18 seconds. As all of these patients but one had been previously digitalized (and usually had an inverted or diphasic *T* wave), digitalis was considered at least partially responsible for the *AV* block. In the case not previously digitalized, the *PR* interval remains long five months later, though no digitalis or quinidin has been given in the interval, here the block is probably organic rather than the result of quinidin administration. One other case still main-

tains a long *P R* interval months after cessation of digitalis and quinidin. Of the others, three, later, became normal in length, one is still under observation and in the other eight fibrillation recurred before the persistence of the *A V* block could be estimated.

In ten cases ectopic beats persisted after restoration of normal mechanism, such cases tended to relapse to fibrillation early, only one still maintaining sinus rhythm.



Fig 6—Electrocardiogram of N P. *a* Auricular fibrillation (before quinidin), Lead II. *b* Auricular fibrillation. Intraventricular block. Lead II. *c* Auricular flutter. Lead II. *d* Normal rhythm. Lead II.

Cases with “fine” and “coarse” fibrillation gave equal percentages of restoration (68 per cent) in the sixty-three cases in which the type was noted.

*Untoward Results*—Transient, unimportant toxic symptoms, disappearing on cessation of the drug appeared in many cases, the most common, in order of frequency, were headache, tinnitus, nausea, vertigo, disturbed vision, vomiting, palpitation and diarrhea. General malaise, precordial pain, nervousness and drowsiness occurred in one or two cases, possibly as effects of quinidin.

In five cases, or 66 per cent, more or less serious untoward results occurred (Table 1). In one case quinidin produced a "fixed flutter," in which digitalis later induced a four to one block, while the resulting regular slow ventricular rate should theoretically have been as satisfactory as a slow ventricular rate in fibrillation; the patient showed increased cardiac symptoms for some time. In one case quinidin produced a "fixed flutter" which persisted as flutter with a ventricular rate of from 140 to 160, with increasing failure until death fourteen days after its onset. Necropsy showed in addition to marked congestive failure pulmonary embolism, presumably from auricular thrombi as foci. It is probable that the production of such "fixed flutter" can be avoided by the cessation of quinidin within twenty-four hours after the onset of the flutter. In one case a transient peripheral unimportant embolism followed the restoration of normal rhythm, the circulation was unaffected and this patient was much benefited by the treatment. One patient died suddenly a few hours after normal rhythm appeared, no

TABLE 1—UNTOWARD RESULTS

	Number of Cases
Fixed flutter—4 to 1 block, patient little harmed	1
Fixed flutter—Pulmonary embolism death	1
Embolism—Peroneal artery, unimportant	1
Sudden death—? embolism, no necropsy	2
	<hr/> 5 (66%)

necropsy was permitted. In the fifth case, the patient had been restored to normal rhythm for several days and then relapsed to fibrillation. Digitalis was begun and three days later she died quite suddenly. No necropsy permission was obtainable.

The scarcity of necropsies in such cases of sudden death under quinidin is unfortunate. The most likely cause of death is massive pulmonary or cerebral embolism. If ventricular fibrillation were responsible, as has been suggested, one would have expected the second of our two patients to have died at the time quinidin was at its maximal concentration and not three or four days later. In cases in which normal rhythm is produced, the lengthening of the refractory period that breaks up the auricular circus is predominant,<sup>6</sup> it does not seem likely that in such a case the drug induces ventricular fibrillation. The answer must come from necropsies and from electrocardiograms at the moment of onset—if more such unfortunate cases occur.

All five of the cases in which serious untoward results occurred had congestive failure and, on admission, a history of one or more periods of such failure in the past was given. Three of the patients had fibrillation of more than a year in duration. That this is the type of case likely to develop untoward results will be noted later.



*Benefit from Restoration of Normal Rhythm*—In some of the cases the benefit from the restoration of normal rhythm was so striking that it was unquestionable. In others, the persistence of the effect of previous digitalization had to be taken into consideration in estimating the part played by quinidin. In cases without objective failure, the temperament of the patient had to be considered in evaluating the subjective improvement noted. Vital capacity readings were of value and usually corresponded to the other clinical evidence of improvement. In noting benefit from quinidin (Table 2) all these factors have been taken into consideration.

GROUP 1 (Table 2)—Two of the five cases not digitalized before quinidin showed what was considered definite improvement from restoration of normal rhythm.

GROUP 2—Four cases failing to respond to adequate doses of digitalis and presenting tachycardia, objective congestive failure, or both

TABLE 2—BENEFIT FROM QUINIDIN

Group	Previous Digitalization	Response to Digitalis	Normal Rhythm by Quinidin	Relapse	Benefit from Quinidin	Number of Cases
1	None		Yes	No	Moderate to marked	2
2	Yes	Poor or none	Yes	No	Moderate to marked	4
3	Yes	Good	Yes	No	Moderate to marked	15
						21(28%)
4	Yes	Good	Yes	No	Slight or none	7
5	Yes	Usually good	Yes	Yes	Slight or none	23
6	Yes	Usually good	No		None	24
						54(72%)

when quinidin was begun, showed marked improvement from restoration of sinus rhythm with slowing of the heart and disappearance of the congestive failure. In two of these the effect was striking.

GROUP 3—Fifteen cases responding moderately or well to digitalis presented definite additional improvement after the reestablishment of normal rhythm. In cases with objective failure persisting after digitalization, this diminished or disappeared. One case is particularly worthy of mention. A physician, whose ventricular rate had been well controlled by digitalis for months, had, nevertheless, been forced to give up his practice because of dyspnea and palpitation on slight exertion. Following the restoration of normal rhythm, he resumed his practice and has continued active work since that time. As he had no objective failure, it is possible that part of the limitation of activity he suffered prior to quinidin was the result of his mental reaction to a knowledge of heart disease, in this case it seems unlikely, but even so the fact remains that through quinidin a valuable man has returned

to activity in his community. This is one of the types of cases most favorable for the use of quinidin.

Twenty-one patients, or 28 per cent, received from moderate to marked clinical improvement from quinidin. It is to be noted that of these, sixteen had fibrillation of less than one year's duration and the majority of less than six months', also that in all but four of these cases the benefit was additional to that obtained from digitalis. It may reasonably be assumed that if 28 per cent of the cases are benefited in a largely unselected series, a considerably larger percentage would be obtainable in a group of selected cases.

*Advantages of Normal Rhythm*—The relative utility of quinidin or quinidine after digitalization and digitalis alone in cases of auricular fibrillation depends on the relative efficiency of the heart when auricles and ventricles beat regularly in sequence and when there is no auricular systole but a slow ventricular rate (as in the digitalized fibrillating heart).

From the clinical point of view the cases of Group 3 (Fig 6) suggest the greater efficiency of the heart in normal rhythm. Recently, Stewart and Carter<sup>16</sup> have reported some interesting observations on blood gases before and after restoration of normal rhythm. Their findings point to a greater efficiency of the cardiorespiratory mechanism under normal rhythm than with a fibrillation, even if the ventricular rate is slow in the latter case.

From an experimental point of view, estimation of cardiac efficiency is difficult and none too accurate. Working with animals several investigators compared cardiac efficiency in fibrillation and normal rhythm, taking cardiac output or blood pressure changes as the criterion of cardiac efficiency. In most cases, however, they dealt only with fibrillation in which the ventricular rate was rapid, a condition not quite comparable with the slow heart of digitalized auricular fibrillation in man. For this reason Lewis' conclusions<sup>17</sup> that the decreased efficiency in fibrillation was simply a factor of increased ventricular rate are not entirely applicable to the present problem. Gesell<sup>18</sup> produced a slow ventricle by blocking *AV* conduction in his fibrillation experiments and concluded that the lowered efficiency of the fibrillating heart resulted from the absence of auricular contractions. Lewis stated that faults in Gesell's technic vitiated the value of his conclusions. More

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16 Stewart, H. J., and Carter, E. P. Blood Gases in Auricular Fibrillation and After Restoration of the Normal Mechanism, *J. A. M. A.* **78** 1751 (June 3) 1922.

17 Lewis, T. J. *Exper. M.* **16** 395, 1912.

18 Gesell, R. A. *Am. J. Physiol.* **29** 32, 1911.

recently Eyster and Swarthout,<sup>19</sup> in experiments similar to those of Lewis, concluded that auricular fibrillation and flutter "produced a variable reduction in the volume output of blood from the ventricles

the effect greater in fibrillation than in flutter and mainly due to the irregularity of the ventricles and to the high percentage of premature and abortive beats, rather than to the fast ventricular rate"

Many patients who have fibrillation live for years, a large percentage of cardiac patients dying have fibrillation. Can we prolong the lives of these patients by restoration of normal rhythm? Years of observation may or may not give us the answer. Many patients with auricular fibrillation live in great discomfort and with markedly restricted activity despite digitalis. That in many such cases restoration of normal rhythm promotes comfort and increases the ability of the patient to carry on a more normal life seems quite certain. In favorable cases in which relapse is less likely, the quinidin cases seem to need no more, perhaps less supervision than digitalis cases. By the restoration of normal rhythm with quinidin we have not removed the underlying heart disease on which the fibrillation is based, but often the precipitating cause for the fibrillation—thyrotoxicosis, acute infection, overexertion, emotional strain, etc.—is long since past. Perhaps, after regaining sinus rhythm, we may be able to guard the patient against further precipitating cause.

*Other Observations*—In the thirteen cases in which teleroentgenograms were taken before and after restoration of normal rhythm, no constant change in the shape of the heart was made out and measurements including the Von Zwaluwenburg auriculoventricular ratio<sup>20</sup> showed no significant changes.<sup>21</sup>

The white blood count in forty-three cases followed showed no significant changes during quinidin administration.

#### UNTOWARD RESULTS WITH AND WITHOUT QUINIDIN

A number of serious untoward results have been reported under the use of quinidin in auricular fibrillation. Of these, embolism and sudden death have been most frequent. That embolism occurs in fibrillation under ordinary treatment not including quinidin is well known, but its frequency is possibly not generally realized. It was, therefore, of interest to compare the frequency of embolism and other

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19 Eyster, J. A. E. and Swarthout, E. C. Experimental Determination of Influence of Abnormal Cardiac Rhythms on Mechanical Efficiency of Heart, *Arch Int Med* **25** 317 (March) 1920.

20 Van Zwaluwenburg, J. G. *Am T Roentgen* **7** 1, 1920.

21 We are indebted to the roentgen-ray department at the Massachusetts General Hospital and to Dr. D. S. Dan in particular for cooperation in the roentgen-ray work.

untoward results under quinidin in 484 cases of fibrillation reported (including the present series) with the frequency of embolism in 200 consecutive cases of auricular fibrillation at the Massachusetts General Hospital not receiving quinidin. Each series includes some cases in which no necropsy was obtained to confirm the diagnosis, but as far as possible the same criteria were used in each group (Tables 3 and 4).

Of the nine patients (4.5 per cent) of the nonquinidin group that suffered embolism while in the hospital, one suffered sudden death (clinically similar to the sudden death under quinidin), although having

TABLE 3—UNTOWARD RESULTS IN CASES TREATED WITH QUINIDIN

484 Cases (+)	Number of Cases
Fixed flutter with embolism (present series)	1
Embolism. Died 3 patients, recovered 2 patients (present series, Ellis and Clarke Kennedy, <sup>8</sup> Johns Hopkins, <sup>22</sup> Wilson and Hermann <sup>12</sup> )	5
Sudden death (present series, Benjamin and Von Kapf, <sup>7</sup> Sappington, <sup>11</sup> Hewlett and Sweeney, <sup>13</sup> Johns Hopkins <sup>22</sup> )	6
Possible embolism as cause of death (Bergmann, <sup>20</sup> Benjamin and Von Kapf <sup>7</sup> )	3
Respiratory paralysis (Frey <sup>4</sup> )	2
Miscellaneous. Collapse, increased failure (Frey, <sup>4</sup> Lyster and Fahr, <sup>9</sup> Hass, <sup>10</sup> Hewlett and Sweeney <sup>11</sup> )	4
Fixed flutter (present series)	1
	15 3.1%
	22 4.5%

TABLE 4—EMBOLISM IN CASES NOT TREATED WITH QUINIDIN—200 CASES

	Number of Cases
Embolism while in the hospital	9 (4.5%)
Entered hospital following embolism	7 (3.5%)
Recovered from embolism	6
Died. Sudden death, probably embolic	1
Embolism immediate cause	5
Embolism only partly cause	4

comparatively good circulation. No necropsy was obtainable in this case to confirm the clinical diagnosis of pulmonary or cerebral embolism. Besides these nine cases an additional seven cases, or 3.5 per cent, entered the hospital following embolism. In comparison with the quinidin cases these last cases should not be included.

In the 484 quinidin cases reported in the literature, the total serious untoward results totaled twenty-two cases, or 4.5 per cent, this included nine cases of embolism and six cases of sudden death probably due to embolism. If the latter are included as cases of embolism there were fifteen cases of embolism, or 3.1 per cent. Including the cases reported by Sappington,<sup>11</sup> by Wilson,<sup>12</sup> and the two Johns Hopkins cases,<sup>22</sup> the total number of cases treated by these investigators was not known so that the percentage of untoward results given is actually a little high in this respect.

Such comparison of untoward results in cases with and without quinidin is not intended to suggest that quinidin is not responsible for such effects. The chronologic relationship between restoration of normal rhythm and embolism or sudden death forces the conclusion that the changed mechanism is responsible. Probably the newly arisen contraction of the auricles forcing out auricular thrombi into the circulation produces the emboli and thus also the sudden deaths. That the percentage of untoward results under quinidin as given here is too low is quite possible, as some cases may not have been reported or included here. On the other hand, two of the cases that are included should, perhaps, have been omitted, the case of Haass<sup>10</sup> (collapse under quinidin) because the drug was given intravenously, and one of Benjamin and Von Kapff<sup>7</sup> which I myself considered not the result of quinidin. So it seems justifiable to conclude that embolism is at least not much more frequent under quinidin treatment than under ordinary therapy. Sudden death, however, is considerably more frequent (12 per cent in quinidin cases as compared with 0.5 per cent in the others).

Study of the twenty-two cases in which untoward results occurred under quinidin, in hope of determining the type of case likely to develop such effects, was rendered difficult by incompleteness of data available in some cases. However, two factors were outstanding and suggestive. A high percentage of the cases presented auricular fibrillation of long standing and an even higher percentage showed objective congestive failure at the time of treatment, in the past, or both. It seems reasonable to suppose that both these factors favor auricular thrombosis and may thus be indirectly responsible for embolism.

#### OBSERVATIONS OF PREVIOUS INVESTIGATORS IN CASES OF AURICULAR FIBRILLATION

Most of the observations made in this series of cases of fibrillation treated with quinidin agree with those of previous investigators. The importance of the duration of fibrillation and presence of congestive failure in determining the response to quinidin has been noted by most of the investigators who studied large series of cases. Frey<sup>4</sup>, Oppenheimer and Mann,<sup>23</sup> and Hewlett and Sweeney<sup>18</sup> referred particularly to the first factor and Frey, Benjamin and Von Kapff,<sup>7</sup> and Hamburger<sup>24</sup> to the latter. Bock,<sup>25</sup> reporting thirty-five cases, laid emphasis on the value of rationing in insuring the maintenance of normal rhythm.

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23 Oppenheimer, B. S., and Mann, Hubert. Clinical Experience with Quinidin in Auricular Fibrillation, *J. A. M. A.* **77** 1800 (Dec. 3) 1921.

24 Hamburger, W. W. Effects of Administration of Quinidin Sulphate in Auricular Fibrillation, *J. A. M. A.* **77** 1797 (Dec. 3) 1921.

25 Bock, G. *Med. Klin.* **17** 1052, 1921.

Frey, in particular, concluded that there was great relief to the patient with restoration of normal mechanism. Nearly all investigators favor previous digitalization in cases with failure and apparently consider that this does not hinder the action of quinidin. The observation of Bock that the drug is particularly indicated in hypertonia and peripheral arteriosclerosis was not confirmed by the observations of this series. The observation of one writer that valve lesions were unfavorable to restoration was not confirmed.

#### QUINIDIN IN PAROXYSMAL FIBRILLATION AND FLUTTER

At the Massachusetts General Hospital eight cases of paroxysmal auricular fibrillation and one case of paroxysmal auricular flutter have been treated with quinidin. Because of the variability in frequency and length of paroxysms without treatment, conclusions should only be drawn in this type of case after long periods of observation. Hence, a detailed report of these cases will not be made at this time.

After some experimentation with dosage 0.4 gm of quinidin sulphate daily seemed the average effective dose. If an attack occurred in spite of this dosage two or three similar additional doses at two hour intervals were given at the onset of the attack. This daily dose continued for a period of months in several cases and failed to produce any observable ill effects, except transient deafness in one case.

In the one case of paroxysmal flutter treated, quinidin was ineffective and was discontinued. In two of the cases of paroxysmal fibrillation the attacks have almost completely ceased since the administration of quinidin. These patients are most enthusiastic.

Four other patients under shorter periods of observation seem much improved. In the other two cases, the data are at present incomplete. The observations to date give the impression that quinidin will prove of much value in the treatment of paroxysmal auricular fibrillation.

*Notes on Cases of Premature Beats*—Only three cases of premature beats (in absence of fibrillation) have been given quinidin, in one no benefit was obtained, in a second the abolition of the premature beats seemed to be associated with a rise in ventricular rate and reappeared as the rate decreased, in the third case quinidin seemed of definite value. It is to be noted that in ten of the cases of "permanent" auricular fibrillation, ectopic beats persisted after the restoration of normal rhythm and this despite the considerable dosage of quinidin that had been given.

*Notes on Cases of Heart Block*—Quinidin given in one case of complete *AV* heart block produced no observable effect, toxic or therapeutic. In one case of partial *AV* block quinidin dropped beats became more frequent, and symptoms of the Stokes-Adams type more

marked Two cases of the fibrillation series and one of the premature beat cases showed bundle branch block before the administration of quinidin, this showed no change under the drug Quinidin produced transient bundle branch block in two cases and intraventricular block of the aberration type in four cases of the fibrillation series

The drug seems to be of no value in heart block and may, on the contrary, be distinctly harmful

#### SUMMARY AND CONCLUSIONS

*A Nonparoxysmal ("Chronic," "Permanent") Auricular Fibrillation and Flutter* —1 Of the seventy-five largely unselected cases of nonparoxysmal auricular fibrillation or auricular flutter in this series, approximately two-thirds were restored to normal rhythm by quinidin and approximately one-third (twenty-six cases) still maintain normal rhythm

2 Sex is not an important factor in determining restoration or maintenance of normal rhythm

3 Patients of different ages respond about equally well to quinidin

4 Other factors being equal the rheumatic and arteriosclerotic types of heart disease respond to the drug equally well The presence or absence of valvular disease in itself is not an important factor in determining response to quinidin Too few cases of thyroid etiology have been treated to determine the relative response of these cases

5 The duration of the heart symptoms is of importance as a factor in determining response only so far as it is associated with two other factors the duration of auricular fibrillation and the degree of congestive failure

6 The most important factor in determining both restoration of normal rhythm and its maintenance is the duration of the auricular fibrillation Cases with fibrillation of short duration (under six months) are not only more likely to be restored to normal mechanism but are much more likely to maintain it even without rations, and, as a rule, give the best clinical results

7 The second most important factor in determining response to quinidin is the presence or absence, past or present, of objective congestive failure Cases with objective failure are restored to normal rhythm about as frequently as those without such failure, the former, however, relapse very much more frequently

8 All cases showing objective congestive failure or tachycardia should probably be digitalized before beginning quinidin treatment So far as was observed such digitalization does not hinder the response to quinidin, and by reducing the degree of failure favors response and may prevent untoward results

9 Though most cases responding to quinidin do so with small dosage, many of the most satisfactory cases require large dosage. This is apparently independent of the duration of fibrillation.

10 Proper rationing with quinidin after restoration of normal rhythm will probably reduce the number of relapses.

11 Embolism and sudden death (possibly also due to embolism) occurring under quinidin therapy are probably most likely to occur in cases with fibrillation of long duration and those where there is objective congestive failure at the time or in the past. Hence, the cases most likely to yield serious untoward results are the cases least likely to obtain a maintained normal rhythm from quinidin.

12 A fair percentage of cases, particularly those with recent fibrillation and little or no objective congestive failure, receive definite benefit from restoration of normal rhythm—benefit apparently additional to that obtainable from digitalis alone. The clinical results appear to justify the use of the drug in cases with fibrillation of short duration and with little or no congestive failure. In this type of case untoward results are probably no more common than under the other methods of treatment. For the present quinidin should probably not be used in a routine way in other types of cases. For the present, at least, quinidin should be used in hospitals where careful observation and electrocardiographic control is possible.

*B Paroxysmal Auricular Fibrillation*—Quinidin will probably prove of much value in the prevention and treatment of paroxysmal auricular fibrillation.

*C Premature Beats and Heart Block*—The data at present available are inconclusive regarding the value of quinidin in treating cases with premature beats.

Quinidin is not indicated for the treatment of heart block.



# ENLARGEMENT OF HEMAL NODES\*

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BROOKLYN, N Y

Extraordinary enlargements of the hemolymph or hemal nodes are extremely rare. These structures, normally present in the human body, almost always of minute size, are usually overlooked in the postmortem examination. Comparatively few references are found in the literature calling attention to these most interesting tissues. They were first described by Lydig in mammals, <sup>1</sup> e., in the hog and sheep, in 1857, and by H. Gibbs in the human being in 1884. The results of systematic examination for these bodies in the human being were first described by Warthin<sup>1</sup> in 1901, and Meyer<sup>2</sup> made an elaborate study of these bodies in the sheep in 1908. In the article by Warthin passing mention of hemolymph nodes is made by pathologists of note who regarded them as of no great significance.

The discoverers of these structures named them hemolymph nodes because of their appearance and microscopic structure. Warthin, however, apparently considers the blood vascular elements, both anatomically and functionally, as the predominant characteristics and suggests as a fitter designation "hemal nodes."

These nodes in the normal state exist as small bodies, very tiny in size, deeply imbedded in the prevertebral fat, lying near a large blood vessel, usually a vein. They are situated, as a rule, near the renal vessels, or in the prevertebral fat of the abdomen or mediastinum. In order to demonstrate them, Warthin recommends dissecting out the prevertebral fat en masse and holding it to the light, when the structures become visible as small red streaks or spots of blood. Occasionally they occur as small nodules of soft consistency.

Because of their gross and so-called microscopic resemblance to splenic tissue, they have been regarded by some as spleniculae and, indeed, at least macroscopically, they may resemble accessory splenic bodies very closely. However, their consistency is very much softer and they are much more collapsible than is splenic tissue. In fact, so impressive to some observers is this resemblance, that a splenic relationship, morphologically and physiologically has been ascribed to them.

For a detailed anatomic and histologic description reference should be made to Warthin's work. Briefly, they vary in size from that of a

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\* From the Pathological Department of the Jewish Hospital

<sup>1</sup> Warthin. *Am J Anat* **1** 63, 1901

<sup>2</sup> Meyer. *Anat Rec* **2** 62, 1908

pinhead to a large cherry or almond. Occasionally, because of ruptures they may be surrounded by blood or be imbedded in a blood clot and escape observation for that reason. They are surrounded by fat and are always described as lying in the posterior part of the thoracic or abdominal cavities. They look like congested lymph nodes or accessory splenic bodies. Their shape may be that of the spleen. They are bluish gray or slate in color. On section, the resemblance to splenic tissue is quite marked. The pulp is homogeneous, streaked here and there with trabeculae and spotted with dew drop-like malpighian bodies. The parenchyma is surrounded by a well defined capsule.

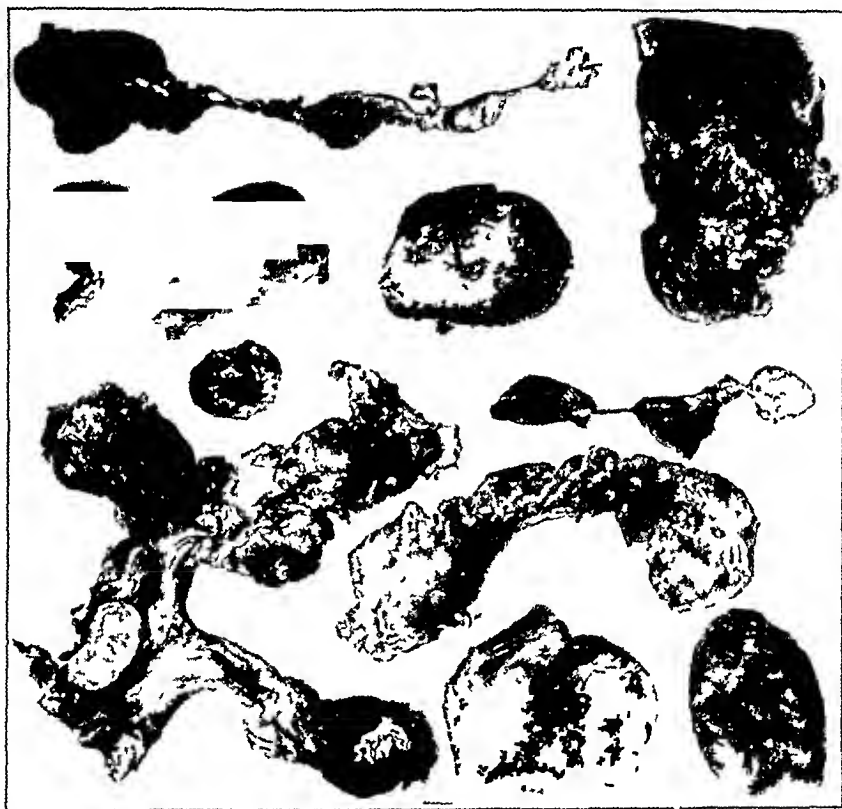


Fig 1—Hemal nodes, natural size

Microscopically, the tissue is seen to consist of numerous blood sinuses lying in a mixture of connective tissue stroma and a variable amount of lymphoid tissue arranged diffusely or in follicles. According to Warthin, the sinuses are traversed by connective tissue fibrils breaking them up into compartments, and in the latter lie red and white blood cells.

Under normal conditions these structures are not numerous and if they are increased in number, many do not attain great size. Symmers<sup>3</sup> describes two cases of tumors of the hemal nodes. In the one case,

3 Symmers, Douglas. Primary Hemangiolymphoma of Hemal Nodes. An Unusual Variety of Malignant Tumor, *Arch Int Med* 28 467 (Oct) 1921

there was a chain of these structures in the pelvis, each from 2 to 3 cm in size, and in the other, metastases through various parts of the body

Because of the unusual size and location of these structures in the following case, it is considered worthy of report

#### REPORT OF CASE

*History*—The patient (69942), aged 14 years, was admitted to the Jewish Hospital in the service of S R Blatteis, Dec 22, 1921. Her condition was desperate, and she died within an hour after admission. The history obtained was unsatisfactory and had no bearing on the findings.

*Postmortem Protocol*—The cadaver was that of a young female, 4 feet 2 inches tall, well developed and well nourished. Opening the thoracic cavity revealed, in the region of the thymus gland, more than twenty varying sized, irregularly shaped, purplish-red, soft masses which appeared collapsed. They were situated in the anterior superior mediastinum and surrounded the ascending portion and arch of the aorta. They were embedded in loose areolar tissue and had a generous blood supply. The largest was 34 by 10 by 8 mm in size, the



Figure 2



Figure 3

Fig 2—Hemal nodes natural size

Fig 3—Hemal nodes, natural size, cross section

smallest was scarcely visible to the naked eye. They varied much in shape, some were spherical, others elliptical, and still others were of a splenic form, with a distinct hilum and lobulations. They were arranged in groups supported by a mass of loose areolar and adipose tissue and were joined to one another by rather large blood vessels. One group was intimately attached by large tributaries to a big vein which entered the superior vena cava. They were all purplish in color with a covering that was smooth and glistening excepting at the part which might be called the hilum and to which the blood vessels were attached. Their consistency was very soft and they felt as though they had been emptied of their contents, the impression being very different than that gained from the palpation of the congested lymph nodes.

*Macroscopic Appearance*—On section, the individual bodies were surrounded by a distinct thick capsule from which trabeculae arose to traverse the parenchyma, but no lobular divisions in most were discernible. The cut surface presented a spongy appearance and was also of a deep purplish color, small dew-drop bodies resembling malpighian corpuscles could be seen in a few areas. The material scraped from the surface was deep purple and apparently consisted mostly of blood.



Fig 4—Hemal node, showing trabeculae from capsule, large blood sinuses  
 $\times 200$



Fig 5—Hemal node, numerous various sized vascular channels, diffuse  
arrangement of lymphoid cells  $\times 100$

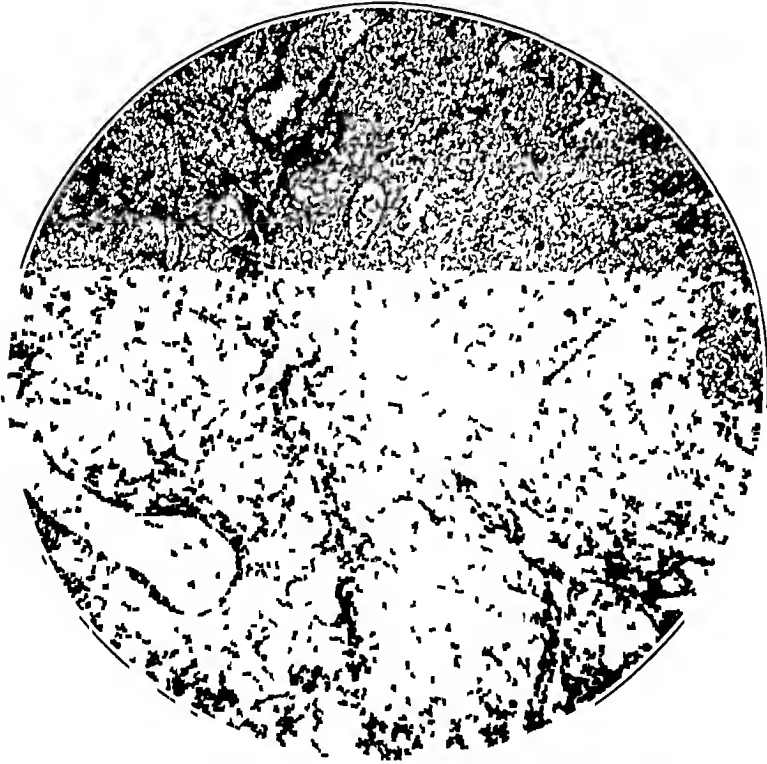


Fig 6—Hemal node showing large sinus with connective tissue fibrils (a)  
Van Gieson stain  $\times 100$



Fig 7—Hemal node, general arrangement of sinuses and contents  $\times 570$

*Microscopic Examination*—Sections were stained by hematoxylin-eosin, Van Giesen and Weigert's elastic tissue methods. Examination under low power reveals a mixture of highly vascular tissue and a number of small round cell collections supported by a variable amount of connective tissue stroma. The tissue is enclosed in a thin capsule composed of a few strands of fibrous connective tissue. From this capsule numerous thin fasciculi penetrate into the depths of the gland, some carrying blood vessels within the bundles. Scattered within some, there are a few collections of small round cells, neither elastic tissue nor the smooth muscle can be demonstrated within the capsule. Lying immediately beneath the capsule are many blood sinuses filled mostly with red blood cells and a few white cells. The remainder of the gland is divided up into varying sized alveoli by rather dense fibrous connective tissue partitions. These spaces are irregular in size and shape, assuming mostly a spherical outline.

The trabeculae are composed of bundles of connective tissue fibers arranged in an irregular fashion and interlacing. The fibers consist of long slender cells containing a few elliptical nuclei, some bundles showing beginning hyalinization. With the Van Giesen stain numerous fibrils arising from these trabeculae are seen to penetrate to within the body of the lobule and there form a connective tissue framework, subdividing the lobule into numerous small spaces (Fig 8). These small spaces also vary in size and shape, being mostly circular. The reticulum is built up apparently from the connective tissue fibrils above described, the spaces actually being lined by flat endothelium. The reticular fibers form walls which are common to adjoining spaces. No elastic tissue or muscle could be demonstrated in these structures. The content of the spaces is blood. Within a few of these spaces are dense collections of small round cells resembling small lymphocytes. These collections are penetrated by small vascular channels in an irregular fashion. In only a very few can a definite reticulum be demonstrated by Van Giesen stain within the bodies of the follicles.

Although they resemble the follicles of lymph nodes, no germinal center or lymph sinuses could be demonstrated. Within the body of these collections are scattered also a few large polyhedral cells containing a large chromatic nucleus, and within the protoplasm numerous pigment granules, they resemble macrophages. The distribution and arrangement of the small round cells vary considerably, according to the part of the node examined although relatively large groups are sometimes seen. In no part does the lymphoid element preponderate. The striking feature of all the sections is the predominant presence of the vascular element, in fact, in some places individual sinuses occupy the areas of several fields under low power magnification, and can easily be seen with the naked eye.

Careful study of numerous sections failed to reveal any evidence of red blood cell destruction. In most instances the red blood cells are intact, and of normal shape and size, there are none of the evidences of red cell phagocytosis or lysis, as usually seen in the spleen. The resemblance to splenic structure is not as close as that described by other observers. There is nothing in the specimen that resembles splenic pulp. The distribution and the character of the connective tissue framework is entirely different and the vascular architecture is in no way comparable to that of the spleen. As a whole the picture is that of a tissue composed of varying sized vascular channels supported by connective tissue reticulum. These channels divide and subdivide until they form either spaces or sinuses formed of a single layer of fibrous connective tissue and lined by a layer of endothelium. Together with this vascular tissue there are small round cells arranged either in organized groups distantly resembling lymph follicles, or diffusely scattered throughout the connective tissue stroma.

Evidences of red blood cell destruction were thoroughly searched for with the means available, but could not be demonstrated. On the contrary as before stated, the red cells seem to present an unusual picture of preservation and in

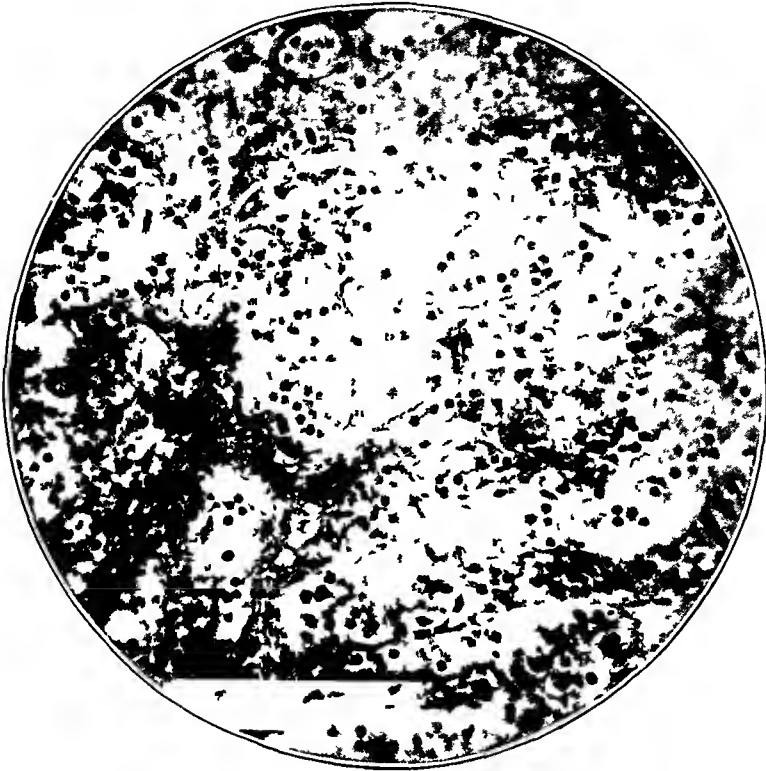


Fig 8—Hemal node, detail of smallest sinuses  $\times 570$

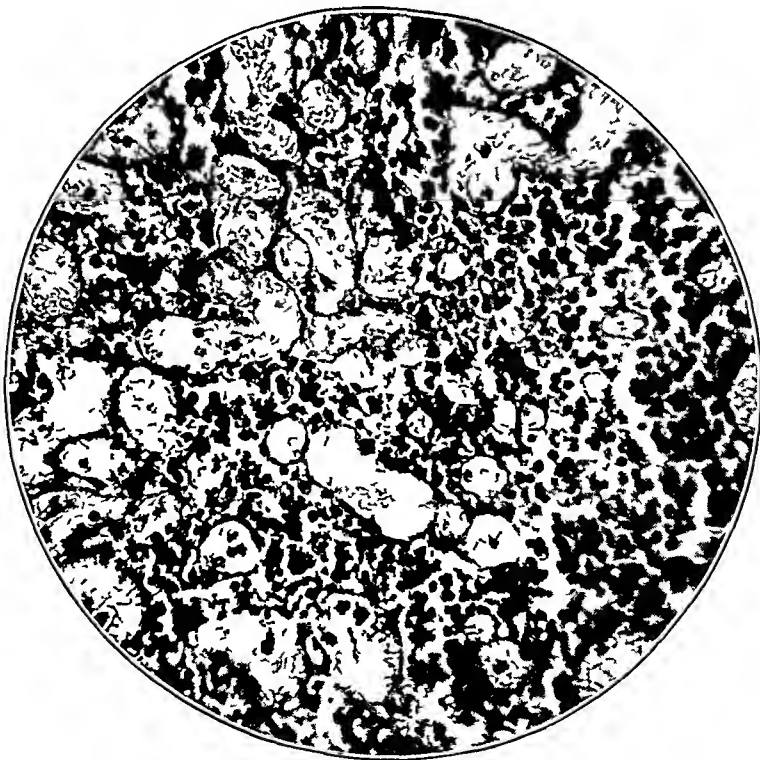


Fig 9—Hemal node, area showing relation of lymphoid cells to blood sinuses  $\times 420$

addition there were noted a few red cells which appear to be nucleated. Unfortunately, because of the method of fixation, special blood stains could not be made. Also, because of the early death of the patient blood studies could not be made. For these reasons this phase of the case could not be studied completely. However, the impression gained from a study of the specimen would be more likely to lead to the conclusion that the picture is certainly not that of a blood destroying organ, but rather that it has to do with blood formation.

In the able description by Warthin he states that the capsule and trabeculae contain smooth muscle and elastic fibers. In our specimen the most diligent search failed to reveal the presence of either of these elements. Perhaps, we must regard this fact as a sign of variation from the normal histology of the node, or as an evidence of pathology.

The remainder of the necropsy showed a very advanced mitral stenosis with the usual pathologic changes incident to the disease, chronic passive congestion of the lungs, liver, spleen and kidneys.

*Comment*—The pathology of hemal nodes has received but scant attention in the literature. The only references available are those of Warthin who mentions changes in these structures, particularly in connection with the blood diseases such as pernicious anemia, leukemia, and Hodgkin's. Symmers reports two cases of neoplasm arising from these structures, one with metastases.

With the incomplete data at hand regarding the history of this case, there is no indication of disease of any sort, excepting that the patient had acute anterior poliomyelitis at 2 years of age. She was perfectly well, attending school up to about a week before admission, when after exposure to inclement weather she was suddenly taken ill and went to bed. She was not treated by a physician and on response to an ambulance call, the intern found her lying in bed in critical shape. She died of cardiac decompensation. It seems hardly likely that the presence of the nodes contributed in any way to the attack which ended her life. In other words, enlargement of these structures could not be explained by compensatory hyperplasia, to which Warthin calls attention in the disturbances of the hematopoietic system. The presence of these masses can then be explained only on one or two bases, either a congenital anomaly or a neoplastic hypertrophy. Examination of the specimen from the standpoint of a neoplasm fails to reveal any evidence of malignancy. There are no evidences of metaplasia, nor were there, after careful search, any metastases.

In addition to the unusual size, the rather unusual location of the nodes must be considered. All observers agree that the most common site of these structures is in prevertebral fat<sup>4</sup>. The only mention of anterior mediastinal growths is that of Symmers' metastatic growths

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<sup>4</sup> Vincent and Harrison. *J. Anat. & Physiol.* **11** 176, 1897. McCallum. *Textbook of Pathology*, 1920, Ed. 2, p. 820.



We have then, to deal with an abnormal increase in size in an unusual location of tissue corresponding to the descriptions of hemal nodes. I am inclined to regard this collection of structures rather in the light of a benign neoplastic hypertrophy of the hemolymph nodes than that of an anomaly. Symmers calls his malignant tumor a primary hemangiolymphoma and regards it as a malignant neoplasm. If the conclusion in this case is correct, similar tumors of benign nature exist

# STUDIES ON THE DETOXIFICATION OF CYANIDS

## I SOME FACTORS INFLUENCING THE DETOXIFICATION OF CYANIDS IN HEALTH AND DISEASE <sup>1</sup>

MEYER BODANSKY, M A

WITH THE COOPERATION OF

MOISE D LEVY, M D

GALVESTON, TEX

In a recent publication, Sullivan and Dawson<sup>1</sup> present data indicating that the sulphocyanate content of the saliva is lower in pellagrics than in normal persons. These authors found that in the active stage of the disease, when the patients are in a more or less cachetic condition, the potassium sulphocyanid (KSCN) formation is low. Sullivan and Dawson suggest that the increased production of potassium sulphocyanid during the convalescent stage of pellagra is due to better assimilation, a higher protein metabolism, and presumably a greater detoxifying power of the system as a whole. They state "Thus the work herein outlined shows that the increased production of sulphocyanate is not closely bound up with total nitrogen but is more probably a product of some endogenous activity perhaps of the synthetic, detoxifying activity of the liver, coupled with a greater assimilation of sulphocyanogenetic complexes."

It has been shown by Grober<sup>2</sup> that the excretion of sulphocyanate is very slight in cachetic or sick persons. This is obviously associated with a diminished absorption of foods. In the prognosis of gastric carcinoma, Fenwick<sup>3</sup> regards the total disappearance of potassium sulphocyanate from the saliva as a grave symptom. The main factor responsible for the diminution in the sulphocyanate concentration of the saliva in this condition, apparently, is due likewise to the impairment of the digestive and absorptive functions. Fenwick considers the formation of potassium sulphocyanate to be dependent also on the metabolic activity of the hepatic cells. He states that derangements in the function of the liver, as in phosphorus poisoning, acute yellow atrophy, and diffuse cirrhosis, are always accompanied by a diminished elimination of sulphocyanates. Finally, in functional disorders of the salivary glands, the sulphocyanate content of the saliva is lowered.

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\* From the Laboratory of Biological Chemistry with the cooperation of the Department of Internal Medicine, University of Texas School of Medicine

1 Sullivan, M X, and Dawson, P R. *J Biol Chem* **45** 473, 1921

2 Grober, J A. *Deutsch Arch klin Med* **49** 243, 1901

3 Fenwick, S, and Fenwick, W S. *Cancer and Other Tumors of the Stomach*, London, 1902, pp 139, 229

Sulphocyanates are very probably formed as a result of the detoxification of cyanids, either ingested as such, or arising in metabolism. According to Gies and Kahn,<sup>4</sup> and Gies, Lieb and Kahn,<sup>5</sup> the administration to dogs of alanine, glyocol, and leucine, is followed by an increased production of sulphocyanate. Willianen<sup>6</sup> found that the ingestion by rabbits of glyocol, creatinin, creatin and adenin causes an increase in the urinary excretion of sulphocyanates. That acetone nitrile, maleic acid nitrile, and similar substances are rapidly converted into thiocyanates has been shown by Lang<sup>7</sup> as well as by Gies and his collaborators. On the other hand, Dezan's<sup>8</sup> investigations on the genesis of thiocyanic acid lead him to the conclusion that the sulphocyanic acid (HCNS), normally excreted by animals, is exogenous in origin. He asserts that only a minute fraction of ingested aliphatic nitriles are capable of conversion into sulphocyanate in the animal organism.

The view expressed by Gscheidlen<sup>9</sup> that sulphocyanic acid is formed in the salivary glands has been questioned by later investigators. Gies considers the salivary glands organs of excretion rather than of secretion. According to this author, the liver is the organ chiefly concerned in the production of sulphocyanate. The earlier investigation of Pascheles<sup>10</sup> demonstrated that the formation of sulphocyanic acid is not limited to the liver. In a number of "in vitro" experiments, it was found that muscle tissue, though less active than liver, likewise was capable of transforming sodium cyanid into sodium sulphocyanate.

Disease is frequently associated with metabolic derangements. For example, abnormal sugar tolerance curves are obtained in a large variety of pathologic conditions. Apparently, this is due to an impairment of the "carbohydrate disposal mechanism" of the body. The possibility suggests itself that in disease other metabolic functions might be similarly affected. If this were true in the case of the cyanid detoxifying function, it would account partially for the low sulphocyanate elimination in disease conditions. An analysis of Sullivan and Dawson's data shows that the average sulphocyanate content of saliva collected in 30 minutes from twenty-one active pellagrins is 1.36 mg. The average elimination of twenty-six convalescent pellagrins was found to be 2.55 mg. Five normal subjects eliminated on an average

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4 Gies, W. J., and Kahn, M. *Dental Cosmos* **55** 40, 1913.

5 Gies, W. J., Lieb, C. C., and Kahn, M. *Dental Cosmos* **56** 175, 1914.

6 Willianen, K. *Biochem Ztschr* **1** 129, 1906.

7 Lang, S. *Arch exper Path u Pharmacol* **34** 247, 1894.

8 Dezan, S. *Arch farm sper* **23** 245, 1917, **24** 113, 193, 1918, **25** 83, 278, 1918, **26** 257, 1919, **27** 134, 1919, **28** 23, 1919.

9 Gscheidlen, cited in Abderhalden, *Textbook of Physiological Chemistry*, New York 1911, p. 250.

10 Pascheles, W. *Arch exper Path u Pharmacol* **34** 281, 1894.

178 mg potassium sulphocyanate (KCNS) in thirty minutes. A number of objections may be raised concerning the validity of conclusions based on the analysis of individual saliva specimens. Daily variations in the sulphocyanate elimination may be quite large. As is well known, smokers excrete greater quantities of thiocyanates than nonsmokers. In Sullivan and Dawson's work there is no indication as to which of the subjects were smokers and which were nonsmokers. It is also to be noted that some of the individuals in the active pellagra group eliminated more sulphocyanate than some of the normals.

In undertaking the present study, our object was to determine whether in disease there is an impairment in the cyanide detoxifying capacity of the organism. As far as we are aware, no functional test has been suggested hitherto for the determination of "cyanid tolerance." The principle of our method is based on the fact that the administration of small doses of potassium cyanid (KCN) results in a rapid increase in the sulphocyanate concentration of the saliva. It is appreciated that the salivary glands are not the only organs concerned in the excretion of sulphocyanate. This substance is excreted also in the urine and bile. Furthermore, the "salivary gland threshold" for sulphocyanates appears to be a peculiarity of the individual. Unless the excretory capacity of the salivary glands is determined adequately, it may be expected that analyses, only of the saliva, would afford insufficient data on which to base any deductions regarding the detoxifying capacity of the organism.

The excretion of sulphocyanates in the saliva after potassium cyanid administration is dependent on the following factors: absorption of the cyanid from the alimentary canal, the capacity of the organism to detoxify the cyanid—radicle, the functional capacity of the salivary glands in excreting potassium sulphocyanate. The first factor may be omitted from consideration because it is known that small quantities of cyanids are absorbed from vascular tissues with extreme rapidity. Furthermore, there is no reason for assuming that different individuals would show significant variations in this respect. If the third factor is controlled by determining the increased salivary elimination of potassium sulphocyanate after its ingestion as such, it becomes possible to study the second factor, namely, the cyanide detoxifying capacity of the organism.

#### METHODS

Accordingly, we adopted the following procedure. On the first day of the test, the subject, after rinsing the mouth with water, collected a specimen of saliva, under the stimulus of chewing white paraffin wax, during a fifteen minute period (from 7:45 to 8 a.m.). At 8 a.m., a gelatin capsule, containing 15 mg potassium sulphocyanate, was

swallowed, and the mouth again rinsed with water. Specimens of saliva were collected, as before, during the following intervals: from 8 15 to 8 30, from 9 to 9 15, from 9 45 to 10, and from 11 to 11 15. No food was eaten before or during the test and the subjects abstained from tobacco. The sulphocyanate content of each saliva specimen was determined, the analyses being made in duplicate.

On the second day of the test, an initial specimen of saliva was again collected between 7 45 and 8 a. m. At 8 a. m. a gelatin capsule, containing 10 mg. of potassium cyanid, was swallowed. If 10 mg. of potassium cyanid were totally converted into potassium sulphocyanate, approximately 15 mg. of potassium sulphocyanate would be formed. Additional saliva specimens were collected during the same intervals as on the first day. For our purposes, it was not necessary to control the diet of the subjects. However, about the same type and quantity of food was eaten during the days of the test.

In the determination of sulphocyanates, an attempt was made first to use the Rupp-Schied<sup>11</sup>-Thiel<sup>12</sup> method as employed by Sullivan and Dawson<sup>1</sup>. This procedure proved too tedious. In the case of saliva specimens of low potassium sulphocyanate concentration, the method was inadequate. The sulphocyanate content of saliva can be determined with a fair degree of precision as well as with relative ease by means of the color reactions with ferric chlorid and hydrochloric acid. In our work, all the specimens collected from a given individual during the day were analyzed simultaneously. In this way it was possible to compare each specimen not only with standard potassium sulphocyanate solutions, but with each other as well.

A stock standard solution was prepared by dissolving 1 gm. of dry, pure potassium sulphocyanate in two liters of water. The standard solutions were prepared by diluting the stock solution (1 cc. = 0.5 mg. KCNS), to suitable volumes. Standard solutions of the following concentrations were prepared:

- 1 Five cc. stock solution diluted to 50 cc. (5 cc. = 0.25 mg.)
- 2 One cc. stock solution diluted to 25 cc. (5 cc. = 0.10 mg.)
- 3 One cc. stock solution diluted to 50 cc. (5 cc. = 0.05 mg.)
- 4 One cc. stock solution diluted to 100 cc. (5 cc. = 0.025 mg.)
- 5 One cc. stock solution diluted to 200 cc. (5 cc. = 0.0125 mg.)

From these standards it is possible to prepare other standard solutions whenever needed. For example, dilution of standard No. 2 with water in the proportion of 3:2 gives a solution, 5 cc. of which is equivalent to 0.06 mg. The colorimetric comparisons were performed as follows. To 5 drops of 5 per cent. ferric chlorid and 4 drops of 1

11 Rupp, E., and Schied, A. *Ber. chem. Gesellsch.* **35** 2191, 1902.

12 Thiel, A. *Ber. chem. Gesellsch.* **35** 2766, 1902.

per cent hydrochloric acid, in a 150 cc casserole, 5 cc of filtered saliva were added. After mixing, the color produced was compared with that obtained by adding standard potassium sulphocyanate solutions to similar quantities of ferric chlorid and hydrochloric acid. This method has proved itself to be entirely adequate for the purposes of this investigation. In view of the fact that substances interfering with the color reaction, such as salicylates, were excluded, no error from this source was possible. Interference due to aceto-acetic acid was not observed in any of the several hundred analyses performed by us. Nevertheless, as an additional measure of precaution, several drops of mercuric chlorid were added before discarding the solutions. The color due to ferric sulphocyanate ( $\text{Fe}[\text{CNS}]_3$ ) is readily dispelled in this way.

In the present investigation, the test was applied to eight normal subjects (medical students) and seventeen patients, including three pellagrins. The results are recorded in Table 1. Examination of the data reveals the fact that the capacity to detoxify small amounts of potassium cyanid was not impaired in the pathologic conditions studied by us. It is to be noted that variations in the initial sulphocyanate concentration of the saliva may occur in the same individual from day to day. As a rule, the elimination of potassium sulphocyanate after potassium cyanid administration approximates that after potassium sulphocyanate ingestion. The rapidity with which potassium cyanid is transformed in the organism is very striking. Within fifteen minutes after the ingestion of this substance, it is absorbed, detoxified, and its elimination in the saliva becomes apparent. In this connection it is to be noted that one of the normal subjects (Lep) showed an unusual delay in the detoxification of potassium cyanid.

The necessity for determining the excretory capacity of the salivary glands is emphasized by the results obtained in the test on another normal subject (Ram). In this case, the initial sulphocyanate concentration was 1.8 mg in 100 cc. After the ingestion of 15 mg potassium sulphocyanate, the maximum increase was obtained in the interval (from 8.15 to 8.30). The potassium sulphocyanate concentration of the saliva was now 2.2 mg in 100 cc, an increase of only 0.4 mg. A similar increase was obtained after the ingestion of 10 mg potassium cyanid. In this instance, the highest concentration was reached during the interval from 9 to 9.15. In view of this and other findings, it appears that like dosages of potassium sulphocyanate or potassium cyanid do not necessarily stimulate equivalent excretory activity on the part of the salivary glands of different persons. We believe that this is one of the chief factors responsible for the wide variation in the sulphocyanate concentration of the saliva in man.

TABLE 1—DATA SHOWING THE EFFECT OF POTASSIUM SULPHOCYANATE AND POTASSIUM CYANIDE ADMINISTRATION ON THE SULPHOCYANATE\* CONCENTRATION OF THE SALIVA

Subject	Time, A M	First Day Influence of KONS			Second Day Influence of KON		
		KONS Ingested, Mg	Volume Saliva, Cc	KONS in 100 Cc Saliva, Mg	KON Ingested, Mg	Volume Saliva, Cc	KONS in 100 Cc Saliva, Mg
Whit Normal (Smoker) Male	7 45- 8 00	15	39	0 70	10	36	1 10
	8 00						
	8 15- 8 30		40	2 00		26	2 20
	9 00- 9 15		32	2 20		45	1 72
	9 45-10 00		47	1 80		44	1 60
	11 00-11 15		38	1 40		40	1 80
Mil Normal (Nonsmoker) Male	7 45- 8 00	15	33	1 40	10	29	1 40
	8 00						
	8 15- 8 30		36	1 56		23	1 90
	9 00- 9 15		34	1 90		23	2 00
	9 45-10 00		30	1 90		28	1 60
	11 00-11 15		27	2 40		22	1 60
Lit Normal (Smoker) Male	7 45- 8 00	15	30	2 60	10	22	4 00
	8 00						
	8 15- 8 30		23	3 00		24	5 00
	9 00- 9 15		19	3 50		16	5 50
	9 45-10 00		19	3 75		18	5 00
	11 00-11 15		18	3 30		26	4 00
Lep Normal (Smoker) Male Chronic con- stipation	7 45- 8 00	15	21	3 00	10	15	2 70
	8 00						
	8 15- 8 30		24	4 00		16	2 50
	9 00- 9 15		35	4 00		52	2 50
			37	4 00		30	3 50
			36	4 50		27	3 00
Ram Normal (Smoker) Male	7 45- 8 00	15	27	1 80	10	29	1 80
	8 00						
	8 15- 8 30		28	2 20		29	1 80
	9 00- 9 15		31	2 00		44	2 20
	9 45-10 00		29	2 00		46	2 00
	11 00-11 15		33	2 00		33	1 80
Ada Normal (Smoker) Male	7 45- 8 00	15	38	4 00	10	40	4 00
	8 00						
	8 15- 8 30		40	4 00		39	4 00
	9 00- 9 15		35	4 40		39	5 00
	9 45-10 00		32	4 40		40	5 00
	11 00-11 15		25	4 40		28	4 50
Guy Normal (Nonsmoker) Male	7 45- 8 00	15	50	1 30	10	45	2 00
	8 00						
	8 15- 8 30		52	1 44		37	2 70
	9 00- 9 15		56	1 40		41	2 92
	9 45-10 00		49	1 68		48	2 20
	11 00-11 15		48	2 00		40	2 40
Col Normal (Nonsmoker) Male	7 45- 8 00	15	67	0 44	10	61	0 80
	8 00						
	8 15- 8 30		52	0 56		60	0 84
	9 00- 9 15		56	0 56		58	1 06
	9 45-10 00		50	0 74		50	1 06
	11 00-11 15		57	0 74		46	1 10
Cole Pellagra Convalescent (Nonsmoker) Female	7 45- 8 00	15	7 5	0 80	10	7 5	1 39
	8 00						
	8 15- 8 30		10 0	1 40		13 0	2 15
	9 00- 9 15		8 0	2 60		6 0	4 75
	9 45-10 00		6 5	2 40		13 0	3 23
	11 00-11 15		7 0	2 00		10 0	3 20
Rob Pellagra, arthritis (Smoker) Male	7 45- 8 00	15	47	0 30	10	53	0 30
	8 00						
	8 15- 8 30		41	0 40		42	0 34
	9 00- 9 15		54	0 42		48	0 50
	9 45-10 00		51	0 80		47	0 60
	11 00-11 15		40	0 70		42	0 76

\* It is probable that the sulphocyanate occurring in the body is not entirely in the form of the potassium salt. For convenience, however, all results have been computed in terms of potassium sulphocyanate.

TABLE 1—DATA SHOWING THE EFFECT OF POTASSIUM SULPHOCYANATE AND POTASSIUM CYANID ADMINISTRATION ON THE SULPHOCYANATE CONCENTRATION OF THE SALIVA—(Continued)

Subject	Time A M	First Day Influence of KCN			Second Day Influence of KCN		
		KCN Ingested, Mg	Volume Saliva, Cc	KCN in 100 Cc Saliva, Mg	KCN Ingested, Mg	Volume Saliva, Cc	KCN in 100 Cc Saliva Mg
Oal	7 45- 8 00		10	0 40		8	0 40
Active pellagra	8 00	15			10		
(Smoker)	8 15- 8 30		7	1 80		9	0 80
Male	9 00- 9 15		10	1 20		5	1 12
	9 45-10 00		7	0 60		4	1 12
	11 00-11 15		7	0 80		4 5	1 00
Joh	7 45- 8 00		60	0 32		45	0 44
Arthritis,	8 00	15			10		
pellagra 2 years	8 15- 8 30		34	0 44		43	0 92
ago	9 00- 9 15		45	0 96		39	1 20
(Nonsmoker)	9 45-10 00		60	0 88		46	1 20
Female	11 00-11 15		35	1 00		30	1 50
Web	7 45- 8 00		22	1 80		33	1 80
Pernicious	8 00	15			10		
anemia	8 15- 8 30		14	2 00		20	2 20
(Nonsmoker)	9 00- 9 15		13	4 40		14	1 80
Male	9 45-10 00		23	2 80		16	5 00
	11 00-11 15		8	2 80		13	3 60
Dal †	7 45- 8 00		18	0 55		10	2 00
Pernicious	8 00	15			10		
anemia	8 15- 8 30		14	0 55		14	3 20
(Smoker)	9 00- 9 15		12	0 65		18	4 00
Male	9 45-10 00		12	1 00		5	4 40
	11 00-11 15		19	0 80		18	4 00
Amun	7 45- 8 00		13	0 60		10	1 30
Leprosy	8 00	15			10		
Female	8 15- 8 30		28	2 40		23	1 80
	9 00- 9 15		23	2 40		20	2 90
	9 45-10 00		22	1 70		27	2 40
	11 00-11 15		21	1 70		27	2 60
Godd	7 45- 8 00		25	1 50		33	2 00
Leprosy	8 00	15			10		
(Smoker)	8 15- 8 30		41	2 20		33	2 80
Male	9 00- 9 15		40	2 40		50	3 40
	9 45-10 00		37	2 40		31	3 00
	11 00-11 15		37	2 00		41	2 80
Cort	7 45- 8 00		37	2 00		20	2 40
Leprosy	8 00	15			10		
Female	8 15- 8 30		25	2 80		30	4 20
	9 00- 9 15		25	3 70		16	3 40
	9 45-10 00		30	3 30		37	3 40
	11 00-11 15		38	3 00		30	3 30
How	7 45- 8 00		38	0 40		36	0 50
Congestion of	8 00	15			10		
liver, passive	8 15- 8 30		41	0 64		31	0 80
(Smoker)	9 00- 9 15		25	0 70		45	1 40
Male	9 45-10 00		24	0 64		35	1 00
	11 00-11 15		33	0 70		30	1 80
Val	7 45- 8 00		34	1 60		28	1 80
Congestion of	8 00	15			10		
liver, passive	8 15- 8 30		34	1 84		31	2 00
Female	9 00- 9 15		35	2 20		29	2 60
	9 45-10 00		34	2 80		27	3 00
	11 00-11 15		30	3 60		28	3 60
O'Br	7 45- 8 00		26	0 56		15	1 10
Cholangitis,	8 00	15			10		
acute, arsenical	8 15- 8 30		31	0 96		38	1 20
(Smoker)	9 00- 9 15		46	0 60		35	1 40
Male	9 45-10 00		33	1 00		17	1 60
	11 00-11 15		43	1 10		52	1 20

† In this patient, the second day's test was applied one day following blood transfusion



TABLE 1—DATA SHOWING THE EFFECT OF POTASSIUM SULPHOCYANATE AND POTASSIUM CYANID ADMINISTRATION ON THE SULPHOCYANATE CONCENTRATION OF THE SALIVA—(Continued)

Subject	Time, A M	First Day Influence of KCNS			Second Day Influence of KCN		
		KCNS Ingested, Mg	Volume Saliva, C c	KCNS in 100 C c Saliva, Mg	KCN Ingested, Mg	Volume Saliva, C c	KCNS in 100 C c Saliva, Mg
Amel	7 45- 8 00		21	1 60		18	2 40
Tuberculous	8 00	15			10		
peritonitis	8 15- 8 30		22	1 80		17	2 40
Female	9 00- 9 15		25	3 50		31	3 00
	9 45-10 00		25	2 40		16	4 00
	11 00-11 15		24	2 00		16	3 00
Jac	7 45- 8 00		20	0 80		23	0 55
Diffuse hepatic	8 00	15			10		
cirrhosis	8 15- 8 30		11	2 60		20	0 80
(Smoker)	9 00- 9 15		6	2 60		9	2 60
Male	9 45-10 00		7	2 80		6	2 80
	11 00-11 15		13	1 0		15	1 40
Will	7 45- 8 00		30	2 00		28	2 70
Arthritis	8 00	15			10		
(Nonsmoker)	8 15- 8 30		31	2 90		24	2 70
Male	9 00- 9 15		37	2 00		25	3 90
	9 45-10 00		28	2 80		28	3 60
	11 00-11 15		16	3 30		33	3 80
Norr	7 45- 8 00		14	2 40		23	3 00
Diabetes	8 00	15			10		
(Nonsmoker)	8 15- 8 30		14	2 20		40	2 00
Female	9 00- 9 15		22	4 00		34	3 00
	9 45-10 00		23	2 80		15	4 00
	11 00-11 15		31	2 00		31	2 00
Derr	7 45- 8 00		31	3 20		22	3 40
Gastric car-	8 00	15			10		
cinoma	8 15- 8 30		30	3 20		23	4 60
Female	9 00- 9 15		21	5 00		24	3 60
	9 45-10 00		33	5 00		21	4 00
	11 00-11 15		32	4 00		26	4 40

Of especial interest are the results obtained in the case of one of the patients (Cal), with acute pellagra, of the systemic type. The administration of 15 mg of potassium sulphocyanate caused an increase from 0.4 to 1.8 mg of potassium sulphocyanate in 100 cc of saliva. This was followed by a gradual decrease. On the other hand, the ingestion of 10 mg of potassium cyanid produced an effect that was not quite as marked. This might be interpreted, perhaps, as an indication of a lowered detoxifying power. We do not believe, however, that the failure to transform the potassium cyanid rapidly was due to a disturbance in the detoxifying activity of the liver or of any other organ, but rather to a deficiency in available mercapto yielding substances. As will be shown in another connection, when the administration of potassium cyanid was preceded by the ingestion of 1 gm of cystin, the patient exhibited a normal ability to detoxify cyanids.

In various hepatic disturbances, we failed to observe any abnormalities in cyanid tolerance. Significant is the fact that the patient with diffuse hepatic cirrhosis (Jac) showed a normal capacity to convert potassium cyanid into sulphocyanate.

Table 2 and Chart 1 have been prepared for the purpose of summarizing the results thus far obtained and for comparing the response of sick and healthy persons to potassium sulphocyanate and potassium cyanid administration. The average initial sulphocyanate concentration was lower in the patients than in the normals. Fifteen minutes after the ingestion of 15 mg of potassium sulphocyanate, there was an average increase of 0.44 mg and 0.54 mg of potassium sulphocyanate

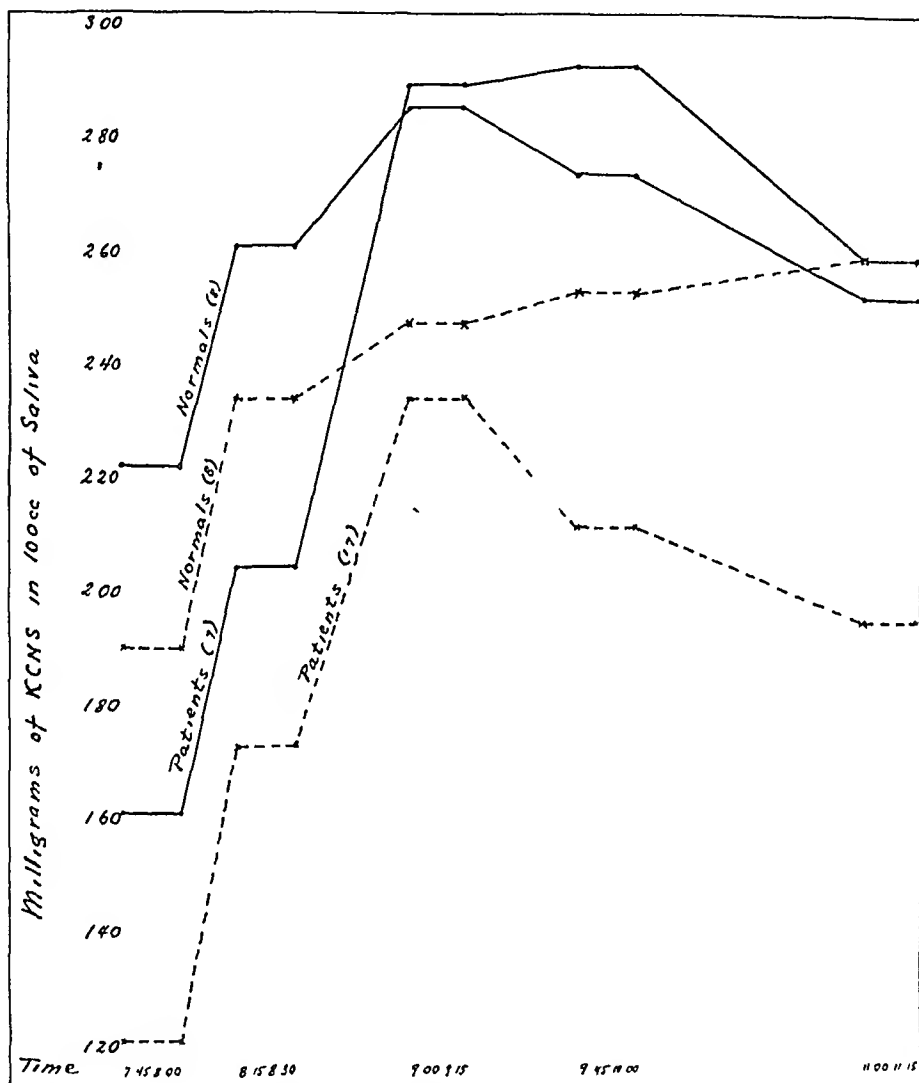


Chart 1—The average curves showing the increased salivary excretion of sulphocyanate in normals and patients following the administration of potassium sulphocyanate and potassium cyanid. (Broken line—effect of potassium sulphocyanate, solid line—effect of potassium cyanid)

in 100 c.c. of the saliva of the healthy and sick persons, respectively. The ingestion of 10 mg potassium cyanid caused, after fifteen minutes, an average increase of 0.39 mg potassium sulphocyanate in 100 c.c. of the saliva of the eight normals. The average increased concentration in the saliva of the seventeen patients amounted to 0.43 mg. At the end

of one hour the average sulphocyanate concentration of the patients' saliva slightly exceeded that of the normals. From this it is to be concluded that in disease the low sulphocyanate elimination is ordinarily due, not to a derangement in the detoxifying capacity of the organism, but more likely to a lowered protein intake and metabolism.

A brief study was made to determine the influence of fatigue of the salivary glands on potassium sulphocyanate excretion. Schneider<sup>13</sup> has

TABLE 2—DATA SHOWING THE RESPONSE OF SICK AND HEALTHY PERSONS TO POTASSIUM SULPHOCYANATE AND POTASSIUM CYANID ADMINISTRATION

Time	Influence of KCNS				Influence of KCN			
	KCNS Ingested, Mg	KCNS in 100 C c Saliva			KCN Ingested, Mg	KCNS in 100 C c Saliva		
		Normals (8)	Patients (17)	Total (25)		Normals (8)	Patients (17)	Total (25)
7 45-8 00	15	1 91	1 22	1 44	10	2 23	1 62	1 81
8 00-8 15		2 35	1 76	1 95		2 62	2 05	2 23
8 15-8 30		2 48	2 35	2 39		2 86	2 90	2 82
9 00-9 15		2 53	2 12	2 25		2 74	2 93	2 87
9 45-10 00		2 59	1 95	2 16		2 52	2 59	2 57
11 00-11 15								

TABLE 3—DATA SHOWING THE PERIODIC VARIATION IN THE EXCRETION OF SULPHOCYANATE IN THE SALIVA

Subject	7 45-8 00		8 15-8 30		9 00-9 15		9 45-10 00		11 00-11 15		Remarks
	Vol C c	Mg in 100 C c	Vol C c	Mg in 100 C c	Vol C c	Mg in 100 C c	Vol C c	Mg in 100 C c	Vol C c	Mg in 100 C c	
Ram	35	1 14	32	1 14	40	0 70	40	0 60	40	0 60	Normal
Gay	41	1 80	41	1 80	38	1 80	47	1 20	42	1 20	Normal
Col	50	0 50	55	0 40	42	0 40	74	0 30	61	0 30	Normal
Cal	13	0 44	10	0 36	10	0 40	7 5	0 40	10	0 40	Pellagra
Web	31	2 60	20	2 40	12	2 60	15	2 60	25	2 80	Pernicious anemia
Dal	12	1 90	9	1 80	10	1 70	9	1 70	14	1 70	Pernicious anemia
Amun	17	1 60	18	1 20	12	1 40	11	1 40	11	1 00	Leprosy
Cort	31	2 20	43	2 00	39	2 30	45	2 00	30	2 00	Leprosy
Val	28	2 10	26	2 10	27	2 30	26	2 30	27	2 20	Congestion of liver
How	38	0 90	45	0 60	35	0 60	41	0 60	53	0 56	Congestion of liver
O'Br	40	1 80	35	1 60	41	1 60	40	1 50	55	1 40	Cholangitis
Amel	15	2 60	20	2 60	17	2 80	17	2 60	16	2 60	Taberc peritonitis
Jac	11	0 72	4	0 68	6	0 68	7	0 60	7	0 60	Dif hepatic cirrho
Wil	35	2 60	47	2 70	46	2 60	30	2 60	35	2 40	Arthritis
Norr	40	2 00	30	2 00	37	2 20	23	2 20	27	2 20	Diabetes
Derr	15	3 00	50	3 00	25	2 90	22	3 00	34	3 00	Gastric carcinoma
Aver	28 3	1 74	30 3	1 65	27 3	1 69	28 4	1 60	30 4	1 56	

shown that the excretion of sulphocyanate may be diminished considerably by prolonged stimulation of the salivary glands. In one case, the flow of saliva was continuously provoked by chewing paraffin. This resulted in a decrease of the potassium sulphocyanate concentration from 0.004 per cent at 8 18 a m to 0.002 per cent at 11 a m. We have determined the periodic variation in the sulphocyanate elimination in the case of sixteen of the twenty-five subjects—three normals and thirteen patients. The saliva was collected during the same intervals as

before, no food being taken on the morning of the test. The results (Table 3) show that usually the initial saliva specimen has a slightly greater potassium sulphocyanate concentration than the specimens collected during the subsequent time intervals. Nevertheless, it is clear that resting the glands aids in the maintenance of the potassium sulphocyanate concentration of the saliva at a fairly constant level.

*Influence of Cystin Feeding on the Detoxification of Potassium Cyanid*—The formation of sulphocyanate in the body appears to be due to a conjugation of cyanid and mercapto groups. It seems that the most important factor is the metabolic supply of the cyanid—radicle. Gies, Lieb and Kahn<sup>5</sup> tested the effect of mercapto yielding substances, including cystin, on sulphocyanate production and distribution in the animal organism. Crude cystin was fed to a dog for seven days. This produced but an insignificant increase in the sulphocyanate content of the urine. However, the liver of the experimental animal was found to contain more potassium sulphocyanid than the livers of the control animals.

We have studied the effect of feeding pure cystin on the formation of sulphocyanate and the detoxification of potassium cyanid in three normal subjects and twelve patients. In determining the influence of cystin, the subject collected an initial specimen of saliva between 7 45 and 8 a m. At 8 a m, 1 gm cystin, mixed with oatmeal or some other cereal, was ingested. Additional saliva specimens were collected during the intervals from 8 15 to 8 30, from 9 to 9 15, from 9 45 to 10, and from 11 to 11 15. On the following day, the effect of cystin on the detoxification of potassium cyanid was determined. An initial saliva specimen was collected again from 7 45 to 8. The cystin was ingested, as before, at 8 a m. From 8 15 to 8 30, a second specimen of saliva was collected. At 8 45, 10 mg of potassium cyanid were administered in a gelatin capsule. Three more saliva specimens were collected during the intervals from 9 to 9 15, from 9 45 to 10, and from 11 to 11 15. The results of the analyses of the saliva are recorded in Table 4.

The ingestion of cystin usually produced no effect on the sulphocyanate concentration of the saliva. In a number of subjects, however, there occurred, as a result of cystin feeding, a marked increase in sulphocyanate elimination. This appeared to be especially marked in the case of a convalescent pellagrin (Cole). If the administration of potassium cyanid is preceded by the ingestion of cystin, the output of sulphocyanate in the saliva is considerably increased. The effect is much more pronounced than that produced when potassium cyanid alone is administered. The averages computed from the results of these experiments are presented in Table 5 and Chart 2. It will be observed

TABLE 4—DATA SHOWING THE EFFECT OF CYSTIN UPON SULPHOCYANATE EXCRETION AND POTASSIUM CYANID DETOXICATION

Subject	Time, A M	First Day Influence of Cystin			Second Day Influence of Cystin + KCN		
		Cystin Ingested, Gm	Volume Saliva, Cc	KONS in 100 Cc Saliva, Mg	Cystin or KCN Ingested	Volume Saliva, Cc	KONS in 100 Cc Saliva, Mg
Whit Normal Male	7 45-8 00	1	28	1 50	1 gm  10 mg KCN	30	1 90
	8 00						
	8 15-8 30		33	1 60		37	1 60
	8 45						
	9 00-9 15		30	1 54		32	3 20
	9 45-10 00		34	1 60		34	3 10
Ram Normal Male	11 00-11 15	1	27	1 30	1 gm  10 mg KCN	38	1 60
	7 45-8 00		27	1 70		36	1 20
	8 00						
	8 15-8 30		31	1 60		27	1 04
	8 45						
	9 00-9 15		40	1 60		32	1 87
Guy Normal Male	9 45-10 00	1	46	1 60	1 gm  10 mg KCN	39	1 80
	11 00-11 15		45	1 52		38	1 70
	7 45-8 00		53	2 30		44	2 00
	8 00						
	8 15-8 30		44	2 30		46	1 70
	8 45						
Col Pellagra Female	9 00-9 15	1	44	2 30	1 gm  10 mg KCN	43	3 10
	9 45-10 00		42	2 10		46	3 00
	11 00-11 15		51	2 00		42	2 40
	7 45-8 00		30	1 52		7	3 86
	8 00						
	8 15-8 30		16	1 52		6	4 03
Rob Pellagra, arthritis Male	8 45	1			1 gm  10 mg KCN		
	9 00-9 15		11	2 20		7	8 57
	9 45-10 00		5	3 00		6	5 00
	11 00-11 15		18	1 28		11	5 18
	7 45-8 00		47	0 44		48	0 30
	8 00						
Cal Pellagra Male	8 15-8 30	1	44	0 44	1 gm  10 mg KCN	43	0 20
	8 45						
	9 00-9 15		43	0 44		45	0 56
	9 45-10 00		35	0 42		43	0 56
	11 00-11 15		42	0 40		43	0 54
	7 45-8 00		7	0 60		5	1 00
Joh Arthritis pellagra 2 years ago	8 00	1			1 gm  10 mg KCN		
	8 15-8 30		5	0 60		12	0 60
	8 45						
	9 00-9 15		5	0 48		15	0 80
	9 45-10 00		6	0 72		10	1 80
	11 00-11 15		5	0 72		9	1 60
Aun Leprosy Female	7 45-8 00	1	38	0 80	1 gm  10 mg KCN	25	0 60
	8 00						
	8 15-8 30		33	0 80		28	0 60
	8 45						
	9 00-9 15		33	0 92		21	1 88
	9 45-10 00		25	1 00		33	1 80
Godd Leprosy Male	11 00-11 15	1	57	0 76	1 gm  10 mg KCN	49	1 76
	7 45-8 00		8	1 60		15	2 20
	8 00						
	8 15-8 30		18	1 40		16	1 80
	8 45						
	9 00-9 15		18	1 50		23	3 40
	9 45-10 00	1	15	1 50	1 gm  10 mg KCN	19	3 70
	11 00-11 15		17	1 20		24	2 70
	7 45-8 00		29	2 60		50	2 40
	8 00						
	8 15-8 30		35	2 60		45	2 40
	8 45						
	9 00-9 15	1	35	2 60	1 gm  10 mg KCN	45	3 60
	9 45-10 00		31	2 80		43	3 80
	11 00-11 15		21	2 80		30	3 50

TABLE 4—DATA SHOWING THE EFFECT OF CYSTIN UPON SULPHOCYANATE EXCRETION AND POTASSIUM CYANIDE DETOXIFICATION—(Continued)

Subject	Time, A. M.	First Day Influence of Cystin			Second Day Influence of Cystin + KCN		
		Cystin Ingested, Gm	Volume Saliva, Cc	KCNS in 100 Cc Saliva, Mg	Cystin or KCN Ingested	Volume Saliva, Cc	KCNS in 100 Cc Saliva, Mg
Cort Leprosy Female	7 45-8 00	1	26	2 50	1 gm  10 mg KCN	40	2 20
	8 00						
	8 15-8 30		33	2 50		13	2 20
	8 45						
	9 00-9 15		41	2 50		25	3 00
	9 45-10 00		36	2 40		25	4 40
How Congestion of liver, passive (Smoker) Male	11 00-11 15	1	26	2 80	1 gm  10 mg KCN	27	4 00
	7 45-8 00		27	0 80		35	1 00
	8 00						
	8 15-8 30		44	1 00		35	0 70
	8 45						
	9 00-9 15		30	0 80		34	0 80
Val Congestion of liver, passive Female	9 45-10 00	1	46	0 75	1 gm  10 mg KCN	12	1 70
	11 00-11 15		44	0 80		27	1 50
	7 45-8 00		31	1 90		28	2 00
	8 00						
	8 15-8 30		30	1 60		26	2 00
	8 45						
O'Br Cholangitis (Smoker) Male	9 00-9 15	1	26	1 40	1 gm  10 mg KCN	27	4 40
	9 45-10 00		50	1 40		26	3 80
	11 00-11 15		21	1 50		27	3 40
	7 45-8 00		37	2 00		42	1 10
	8 00						
	8 15-8 30		25	1 00		36	1 10
Amel Tuberculous peritonitis Female	8 45	1			1 gm  10 mg KCN		
	9 00-9 15		18	2 50		19	3 60
	9 45-10 00		18	2 60		16	5 00
	11 00-11 15		12	3 00		19	4 60
	7 45-8 00		14	2 60		18	2 20
	8 00						
Norr Diabetes Female	8 15-8 30	1	28	2 00	1 gm  10 mg KCN	23	2 00
	8 45						
	9 00-9 15		18	2 50		19	3 60
	9 45-10 00		18	2 60		16	5 00
	11 00-11 15		12	3 00		19	4 60
	7 45-8 00		33	2 60		28	2 00
	8 00	1			1 gm  10 mg KCN		
	8 15-8 30		30	2 00		25	1 60
	8 45						
	9 00-9 15		26	2 00		25	2 70
	9 45-10 00		18	3 60		32	3 80
	11 00-11 15		26	3 60		10	4 80

TABLE 5—DATA SHOWING THE AVERAGE EFFECT OF FEEDING CYSTIN ON THE EXCRETION OF SULPHOCYANATE AND THE DETOXIFICATION OF POTASSIUM CYANIDE

Time	Influence of Cystin				Influence of Cystin + KCN			
	Cystin Ingested Gm	KCNS in 100 Cc Saliva			Cystin or KCN Ingested	KCNS in 100 Cc Saliva		
		Normals (3)	Patients (12)	Total (15)		Normals (3)	Patients (12)	Total (15)
7 45-8 00	1	1 83	1 66	1 70	1 gm  10 mg KCN	1 73	1 74	1 74
8 00								
8 15-8 30		1 83	1 46	1 53		1 45	1 61	1 58
8 45								
9 00-9 15		1 81	1 56	1 61		2 70	2 93	2 80
9 45-10 00		1 77	1 81	1 80		2 63	3 03	2 95
11 00-11 15		1 61	1 69	1 67		1 90	2 92	2 72

that in the case of the normal subjects, cystin produced no effect on the sulphocyanate excretion in the saliva. The gradual slight decrease in concentration was obviously due to fatigue of the salivary glands or to the removal of some potassium sulphocyanid from the circulation. In the patients the effect was somewhat different. The average potassium sulphocyanid concentration of the second specimen was lower than that

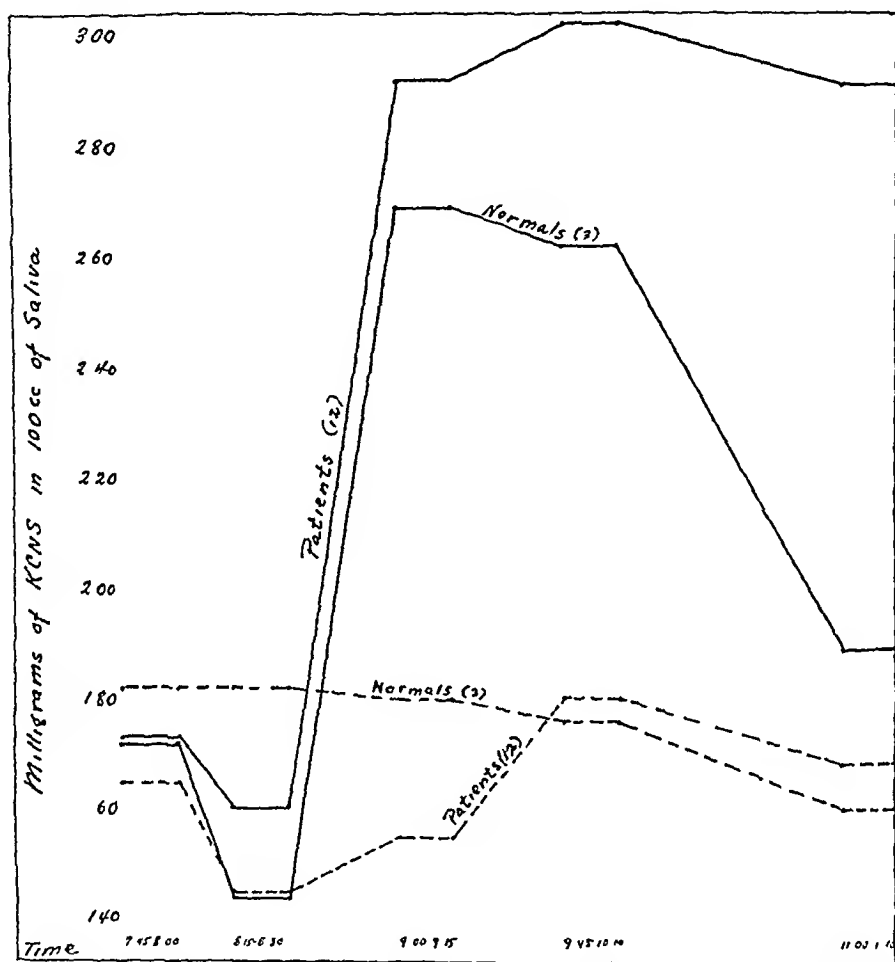


Chart 2—The average curves showing the effect of feeding cystin (broken line) on the excretion of sulphocyanate in the saliva. The influence of cystin on the detoxification of potassium cyanid is represented by the solid lines.

of the initial saliva specimen. Then there followed a measureable increase, the maximum being reached during the interval from 9:45 to 10. The explanation suggesting itself is that the supply of sulphur yielding complexes before the administration of the cystin was insufficient to combine with all the available cyanid radicles. That in disease the cyanid detoxifying power remains unimpaired, provided the supply of cystin is adequate, is made clear by the results of our experiments in which both cystin and potassium cyanid were administered. As in the case of the tests with cystin alone, the potassium sulphocyanid

elimination, in some instances, was lower during the second time interval than during the first. Forty-five minutes were allowed for the partial absorption of the cystin. Ten milligrams of potassium cyanid were then swallowed. In this way an ample available supply both of cyanid and mercapto radicles was assured. Conjugation occurred rapidly, as is evident from the fact that the average potassium sulpho-

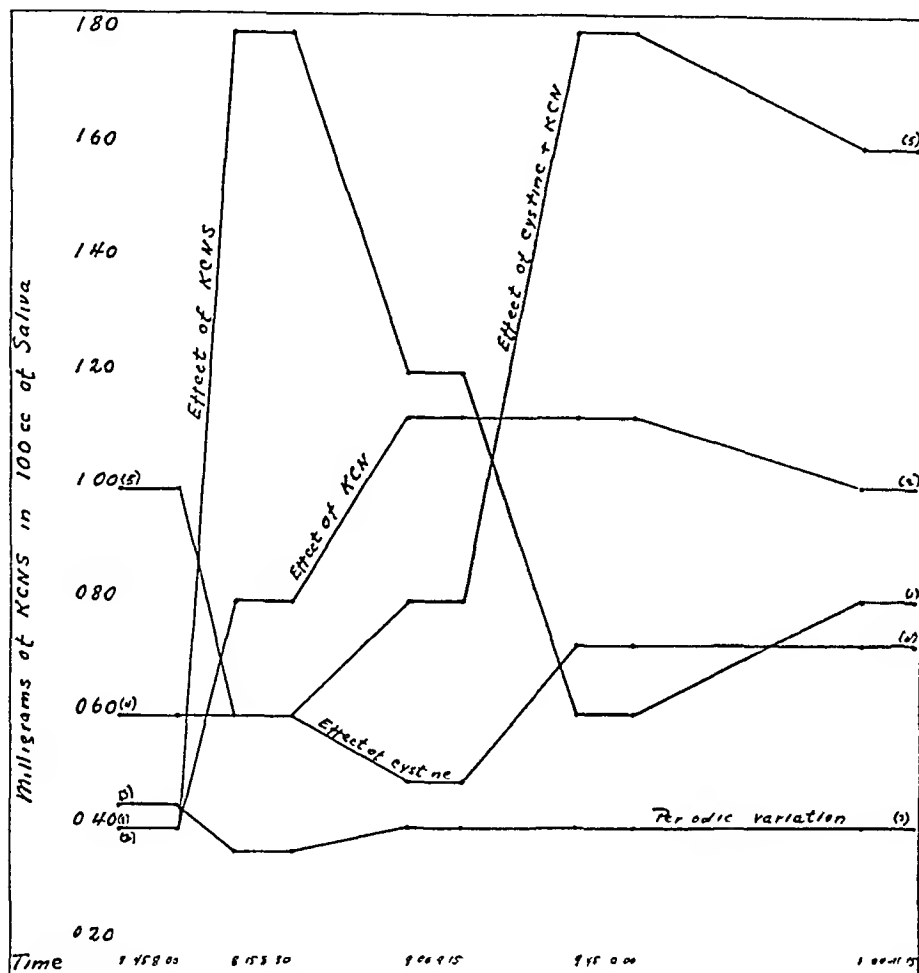


Chart 3—The curves represent the results obtained in a study of the cyanid detoxifying capacity of one of the patients (Cal) with an acute case of pellagra

cyanid concentration of the saliva, collected from fifteen to thirty minutes after the administration of the potassium cyanid, was 83 per cent greater than that of the preceding specimen

It is hoped that this work will be extended to the study of other pathologic conditions. The researches of Reid Hunt<sup>14</sup> are of especial interest in this connection. This author found that the ingestion of thyroid by mice increased their resistance to acetonitrile. On the other hand, feeding mice with parathyroids caused a distinct increase of

14 Hunt, R. J. Biol. Chem. 1 33, 1905



their susceptibility to acetonitrile. In determining cyanid detoxification in man, it is suggested that the five day test be employed. To insure a return to normal of the sulphocyanate content of the saliva on successive test days, the tests may be performed on alternate days or in the following order:

*First Day*—Influence of potassium sulphocyanid (15 mg) on sulphocyanate elimination

*Second Day*—Periodic variation in the elimination of potassium sulphocyanid in saliva

*Third Day*—Effect of potassium cyanid (10 mg) on the sulphocyanate content of the saliva

*Fourth Day*—Effect of cystin (1 gm) on sulphocyanate elimination

*Fifth Day*—Effect of cystin (1 gm) on the detoxification of potassium cyanid (10 mg)

In Chart 3 are represented the results of a five day test, performed on one of the patients (Cal), an active pellagrin. It will be observed that the ingestion of potassium sulphocyanate produced a marked increase in the sulphocyanate concentration of the saliva. This effect was temporary, however. On administering 10 mg potassium cyanid, the potassium sulphocyanate concentration increased about three times. The return to normal in this case was slow. The sulphocyanate concentration of the saliva remained practically constant when neither potassium sulphocyanate nor potassium cyanid were taken. Feeding 1 gm cystin was followed, in this subject, by a slight increase in sulphocyanate elimination. When the administration of 10 mg potassium cyanid was preceded by the ingestion of 1 gm cystin, a rapid increase in the sulphocyanate concentration of the saliva was obtained. In this case the curve indicates a delayed return to the initial sulphocyanate concentration and, therefore, a marked degree of detoxification.

#### SUMMARY

- 1 The detoxification of potassium cyanid was determined in eight normal subjects and seventeen hospital patients.

- 2 Similar dosages of potassium sulphocyanate or potassium cyanid do not necessarily stimulate equivalent excretory activity on the part of the salivary glands of different persons.

- 3 The average sulphocyanate concentration of the saliva was found to be lower in the patients than in the normal subjects. However, after the ingestion of potassium sulphocyanate or potassium cyanid, the sulphocyanate concentration of the patients' saliva increased more rapidly than in the case of the normals.

- 4 Resting the salivary glands during the intervals indicated in our procedure, aids in maintaining the sulphocyanate concentration of the

saliva at a fairly constant level when neither potassium cyanid nor potassium sulphocyanate are administered

5 In normal subjects, cystin produced no effect on the sulphocyanate excretion in the saliva. On the other hand, a slight increase in potassium sulphocyanate elimination was observed in some of the patients.

6 The detoxification of potassium cyanid occurs more rapidly in the human organism when the administration of the cyanid is preceded by the ingestion of cystin.

7 It appears from our results that in certain disease conditions, such as pellagra, the cyanid detoxifying power remains unimpaired, provided the supply of cystin is adequate.

8 A functional test is proposed for the determination of the "cyanid detoxifying capacity" in man.

# STUDIES OF THE BLOOD GASES IN A CASE OF PAROXYSMAL TACHYCARDIA <sup>†</sup>

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During the progress of some studies of the blood gases in auricular fibrillation and after the restoration of the normal sinus mechanism by quinidin sulphate, by one of the authors,<sup>1</sup> a case of paroxysmal tachycardia came under observation and studies of the blood gases were made during the paroxysm and after the return to the normal rate. Barcroft, Bock and Roughton<sup>2</sup> have reported the only similar studies, with an attempt to determine the rate of blood flow and the cardiac output during a paroxysm and in the presence of the normal sinus mechanism. They found in two attacks of paroxysmal tachycardia that the volume output of the heart per minute decreased from one-half to one-third of the normal value, while the ventricular output fell to one-sixth the normal amount. The degree of ischemia was particularly marked in the skin as shown by a marked discrepancy between the oxygen content of blood from the basilic vein and that of the mixed venous blood in the lungs. The depth of respiration was reduced by one-half, but the rate was approximately doubled. No reduction in oxygen saturation of the arterial blood was found. Meakins,<sup>3</sup> from animal experimentation, has concluded that tachycardia, whether regular or irregular, does not in itself produce a decrease in the oxygen saturation of the arterial blood, but that if the tachycardia induces failure of the circulation with pulmonary congestion or edema, a decrease of arterial oxygen saturation will occur.

It was thought of interest to add the studies made of this case to the literature, because the conclusions drawn differ somewhat from those of Barcroft, Bock and Roughton.

## METHODS

The arterial and venous samples of blood were drawn one-half hour after the onset of the paroxysm of tachycardia, while the patient was still in the attack. A second venous specimen was drawn one hour after the end of the paroxysm. After leaving the hospital the patient returned for frequent observation. Blood samples were taken after the patient was put to bed at absolute rest for one-half hour, the

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<sup>†</sup>Working under the tenure of the William Bingham Fellowship in Medicine.

1 Stewart, H J. To be published.

2 Barcroft, J, Bock, A V, and Roughton, F J. *Heart* 9 7, 1921.

3 Meakins, J. *Heart* 9 185, 1922.

time being arranged so that it was at least two hours after the previous meal. The blood was drawn without stasis under albolene as described by Stadie<sup>4</sup> for arterial blood and by Lundsgaard<sup>5</sup> for venous blood. The blood samples were at once analyzed in duplicate, using the "giant" Van Slyke apparatus and the combined method of Van Slyke and

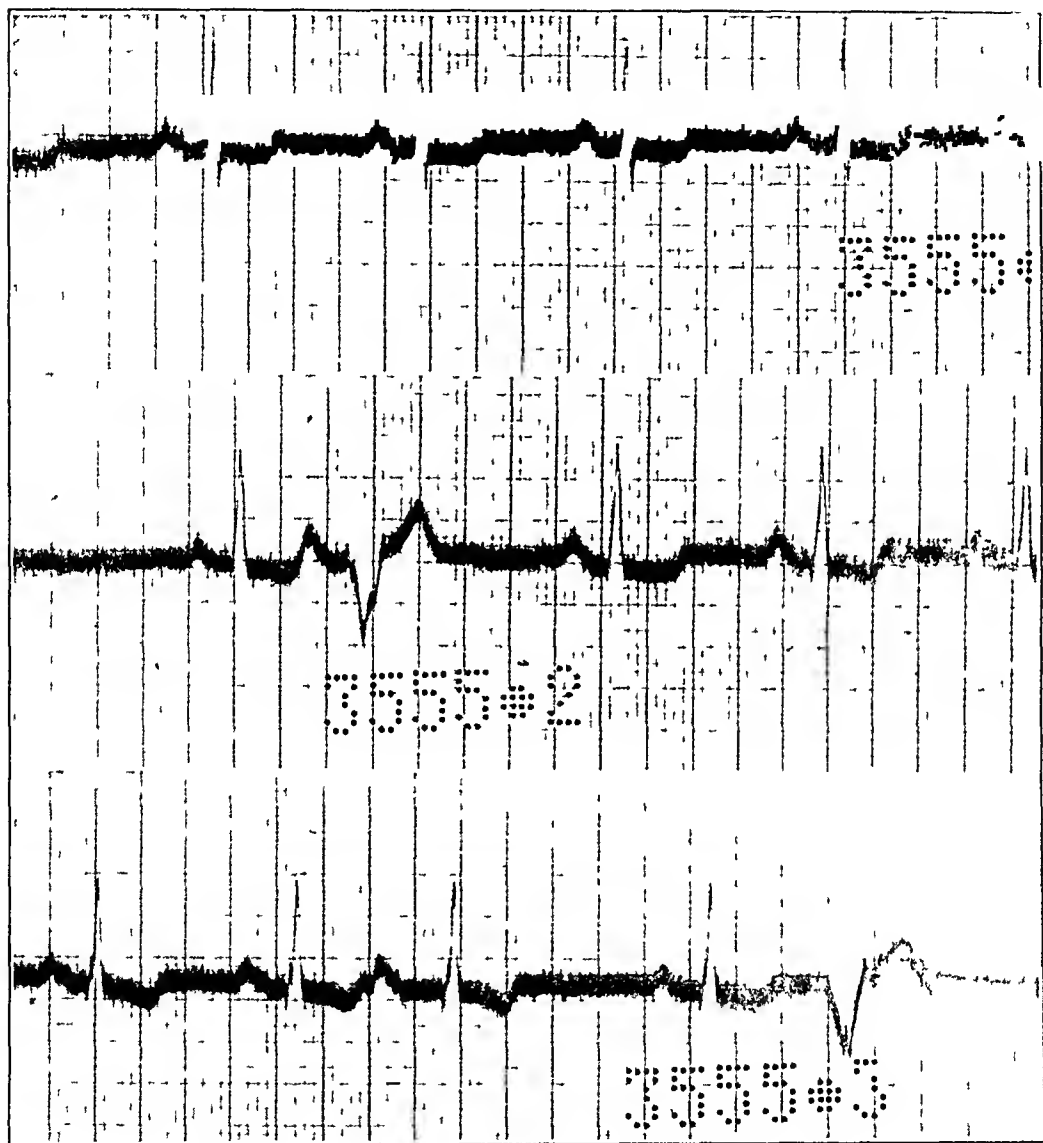


Fig 1—Film shows numerous auricular and right and left ventricular extrasystoles. This interpretation, as well as the interpretation of the succeeding films, was made from a long tracing, which it was not possible to reproduce in full. Taken Jan 27, 1922, soon after admission.

Stadie<sup>6</sup> for determining the oxygen and carbon dioxide on the same sample of blood. The vital capacity was calculated from West's<sup>7</sup>

4 Stadie, W. C. *J. Exper. Med.* 30: 215, 1919.

5 Lundsgaard, C. *J. Biol. Chem.* 33: 133, 1918.

6 Van Slyke, D. D., and Stadie, W. C. *J. Biol. Chem.* 49: 1, 1921.

7 West, H. P. *Arch. Int. Med.* 25: 306 (March) 1920.

formula based on the body surface area, which was estimated from the height-weight chart of Du Bois and Du Bois<sup>8</sup>

#### REPORT OF CASE

E G, female, colored, aged 35, admitted Jan 26, 1922, and discharged March 10, 1922

*Diagnosis*—Chronic rheumatic endocarditis, chronic myocarditis, mitral insufficiency, auricular and ventricular extrasystoles, auricular paroxysmal tachycardia, myocardial insufficiency, chronic tonsillitis

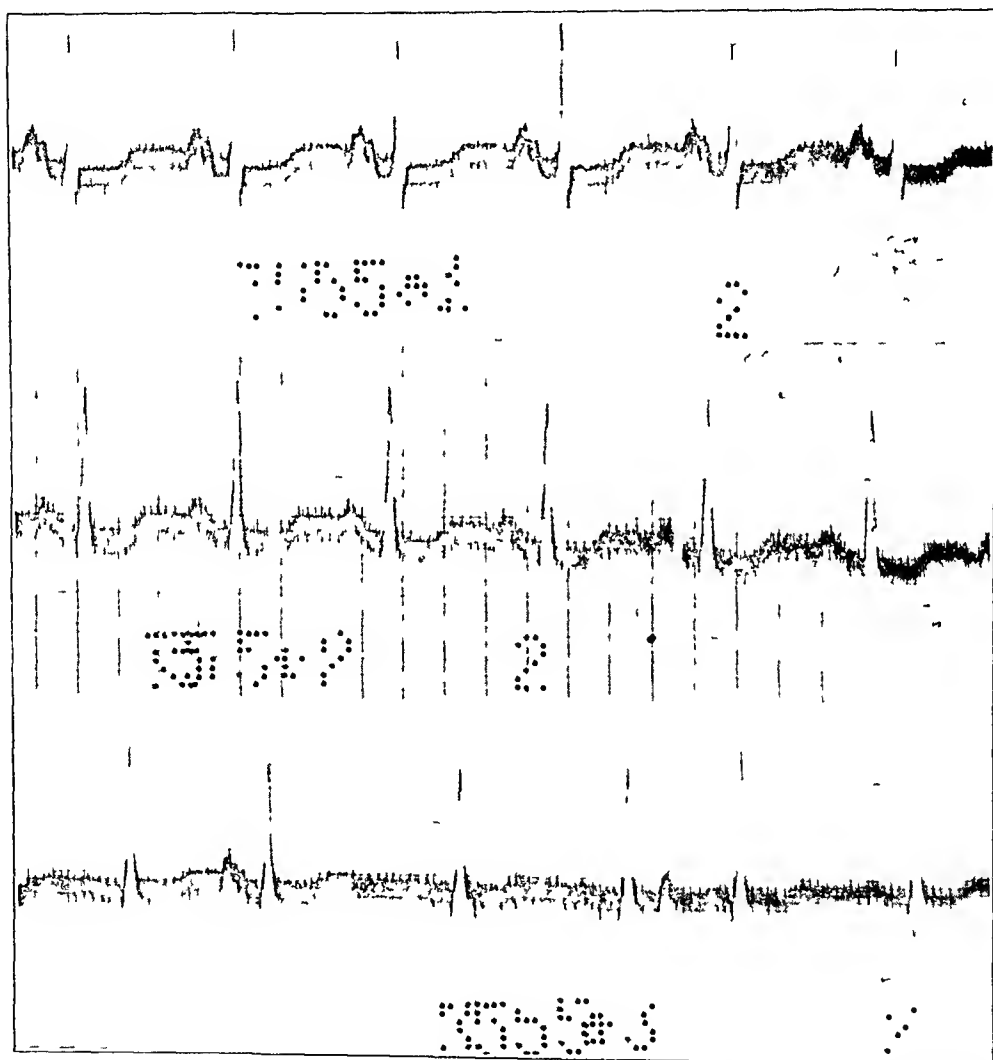


Fig 2—Only occasional auricular extrasystoles Taken after patient had been receiving quinidin sulphate for two days (Feb 7, 1922)

*Complaint*—Attacks of palpitation, difficulty in breathing and swollen legs

*Past History*—Acute rheumatic fever every summer from the age of 9 years up to 10 or 12 years ago Pneumonia at 17, followed by cardiac failure of 26 months' duration Pneumonia again four years ago at which time she was in bed for four weeks A third attack of pneumonia two years ago Frequent attacks of tonsillitis from childhood until ten years ago She has always been

<sup>8</sup> Du Bois, D, and Du Bois, E F Arch Int Med 17 863 (June) 1916

short of breath as far back as she can remember but this has been accentuated in the last seven years. Since then even talking will bring on dyspnea.

*Present Illness*—Began in February, 1921, with palpitation, dyspnea and swelling of the abdomen. The patient had a choking sensation, and numbness in the arms and legs. She was in bed for four weeks and for two months after this she could only walk a few steps. After this she did light work until Thanksgiving, 1921, at which time she had an attack similar to the one in February. Since then she has had frequent attacks of palpitation, described as a "pumping of the heart," and as leaving her chest sore. Attacks are often



Fig 3—Taken during attack of Feb 23, 1922. Auricular paroxysmal tachycardia, rate 198.

preceded by blackness before the eyes. She has had frequent attacks of vomiting, with no relation to meals. Edema has been present since last Thanksgiving.

*Physical Examination*—Temperature, 98.8 F, pulse, 80, respiration, 20. Slightly obese. No general glandular enlargement. Perforated nasal septum. Teeth poorly kept, snags, several missing, some dentistry. Tonsils large, ragged and cryptic. Lungs clear except for a few fine râles at both bases posteriorly. There is a systolic heave of the precordium. No shock, no thrill. The relative cardiac dulness extended 13 cm to the left in the fifth interspace and 4.5 cm

to the right in the fourth intercostal space Cardiac rhythm regular except for numerous extrasystoles There is a prolonged rough systolic murmur over the apex, well transmitted to the axilla and to the base Second pulmonic sound accentuated Blood pressure was 110/75 Liver edge just below umbilicus Liver tender Slight edema of ankles

*Laboratory Findings*—Blood examination negative Vital capacity 33 per cent normal Phenolsulphonephthalein, 50 per cent in two hours The electrocardiogram showed a normal sinus mechanism, numerous auricular and right ventricular extrasystoles (Fig 1) Blood chemistry normal Blood Wassermann negative Urine normal

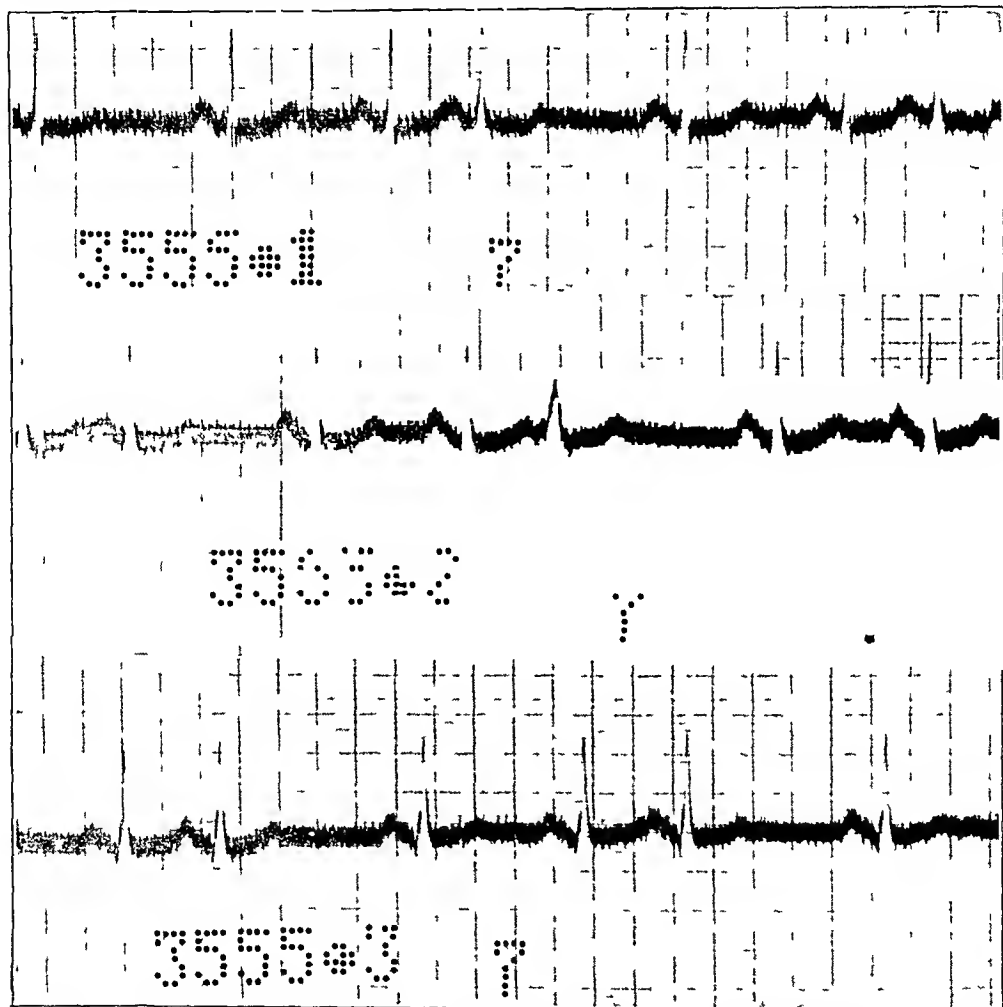


Fig 4—Taken June 16, 1922 Patient has had no quinidin sulphate since leaving the hospital Numerous auricular and occasional right ventricular extrasystoles

*Course and Treatment*—The patient was put to bed on admission Feb 6, 1922, quinidin sulphate therapy was started and February 10, after 27 gm of the drug, the auricular ectopic beats had almost entirely disappeared (Fig 2) February 12 after 2 gm more of quinidin, there were no ectopic beats and the drug was discontinued Although the patient was up several hours each day, no ectopic beats were noted for more than a week, in spite of discontinuance of quinidin sulphate Her vital capacity rose to 61 per cent of normal February 21, there was a rise in temperature to 102.6 F and on the next day the patient's tonsils were injected, the tonsillar glands swollen and tender The

temperature remained elevated for a week. At midnight of February 23, the patient was suddenly seized with dyspnea and palpitation. She became nauseated and vomited. The cardiac rate was 200 on auscultation. This attack lasted for one hour. An electro-cardiogram showed auricular paroxysmal tachycardia (Fig 3). The following day there were occasional extrasystoles. A throat culture showed *Streptococcus hemolyticus*. February 25, the patient had two paroxysms of tachycardia during the course of the morning, with a cardiac rate of 215. Each paroxysm lasted one hour. Electrocardiograms taken February 25 during these attacks were not suitable for publication, but a similar record taken February 23 is published instead (Fig 3).

Blood samples were taken about one half hour after the onset of the second paroxysm February 25. At this time the cardiac rate was 215 and respiration 40, patient was vomiting, veins were distended and there was cyanosis of lips, fingers and ear lobes. No signs of pulmonary congestion. The arterial blood was 85.3 per cent saturated with oxygen and the venous blood 16.7 per cent saturated, coefficient of utilization of the oxygen carrying power, 68.6 per cent, oxygen capacity, 21.14 volumes per cent, arterial carbon dioxide content, 28.07 volumes per cent and venous carbon dioxide content, 46.69 volumes per cent, respiratory quotient, 1.290. One hour after the attack ceased, the venous blood was 68.1 per cent saturated, oxygen capacity, 19.62 volumes per cent, venous carbon dioxide content, 44.51 volumes per cent. Pulse, 80, respiration, 32. Vital capacity, 39 per cent of normal. The patient was comfortable, there was no cyanosis, no signs of pulmonary congestion, and vomiting had stopped. She felt so worn out that she asked to have the arterial puncture delayed.

Between February 25 and March 2, 1922, the patient received 60 gm of quinidin sulphate, during which time there was no further attack and the patient steadily improved. March 5, her vital capacity had risen to 68 per cent normal. Tonsillectomy was advised but the patient refused operation. The patient was discharged in fairly good condition. The patient was seen at frequent intervals after discharge. April 7, 1922, when her heart was slow and regular, her venous blood was 47.7 per cent saturated with oxygen, the oxygen capacity being 18.76 volumes per cent, carbon dioxide content, 55.91 volumes per cent, vital capacity 61 per cent normal. She had had several brief attacks of palpitation since her discharge but was able to carry on her work. June 16, 1922, when the cardiac mechanism was still normal, her arterial blood was 100 per cent saturated, venous blood 45.8 per cent saturated with oxygen, coefficient of utilization, 44.2 per cent, oxygen capacity, 15.81 volumes per cent, arterial carbon dioxide content 42.35 volumes per cent, venous carbon dioxide, 50.50 volumes per cent, respiratory quotient, 0.871. Pulse, 65, respiration, 22, vital capacity 64 per cent normal. No cyanosis, no edema. Slight dyspnea on exertion. Electrocardiogram showed numerous auricular and occasional right ventricular extrasystoles, normal sinus mechanism (Fig 4).

#### DISCUSSION

This case is interesting not only on account of the studies of the blood gases, but also on account of the connection between infection and disturbance of the cardiac mechanism. With normal sinus mechanism the arterial blood was completely saturated with oxygen while the venous blood showed an abnormally low saturation, the coefficient of utilization being 44.2 per cent (the normal range of which is from 20 to 30 per cent). These findings point to an impairment of the peripheral circulation even with a regular cardiac rhythm, or, in other words, to a stagnant or ischemic anoxemia (Barcroft<sup>9</sup>). During the

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9 Barcroft J. Lancet 1 487, 1920



attack of tachycardia there was an anoxic anoxemia and a greatly increased ischemic anoxemia, as shown by the fall in arterial oxygen saturation and the much lower venous content of oxygen, the coefficient of utilization being 68.6 per cent. There were no signs of pulmonary congestion to account for the anoxic anoxemia, and the only cause which suggests itself for the incomplete oxygenation of the blood in the lungs is the reduction in circulatory minute volume brought about by the tachycardia through a greatly decreased output per beat. Barcroft,

TABLE 1—OBSERVATIONS ON THE BLOOD GASES

Date	Mechanism	Oxygen Content		Oxygen Saturation		Coefficient of Utilization	Oxygen Consumption Vol %	Oxygen Capacity Vol %	Hemoglobin %	Carbon Dioxide Content		Difference in Carbon Dioxide Vol %	Respiratory Quotient
		Arterial Vol %	Venous Vol %	Arterial %	Venous %					Arterial Vol %	Venous Vol %		
2/25/22	Paroxysmal tachycardia	18.03	3.52	85.3	16.7	68.6	14.51	21.14	114.3	28.07	46.69	18.62	1.290
1/2 hour after onset													
2/25/22	Normal mechanism		13.26		68.1			19.62	106.1		44.51		
1 hour after end of attack													
4/7/22	Normal mechanism		8.94		47.7			18.76	101.4		55.91		
6/16/22	Normal mechanism	16.08	7.24	100.0*	45.8	44.2	8.84	15.81	85.5	42.35	50.05	7.70	0.871

\* Difference between arterial oxygen content and oxygen capacity is within experimental error

TABLE 2—CLINICAL OBSERVATIONS

Date	Pulse		Respiration		Blood Pressure	Artery Used	Vital Capacity, per Cent Normal	Remarks
	Arterial Puncture	Venous Puncture	Arterial Puncture	Venous Puncture				
2/25/22	215	215	38	40		Right radial		Marked cyanosis, veins engorged, vomiting no râles at lung bases
In attack								
2/25/22		80		32			39	Patient comfortable, no cyanosis
1 hour after								
4/7/22		92		30	125/90		61	No cyanosis, no edema, no râles
6/16/22	60	68	20	24	105/85	Right radial	64	No cyanosis, no edema, dyspnea on exertion, no râles

Bock and Roughton found an arterial oxygen saturation of 96.8 per cent during an attack of paroxysmal tachycardia. They concluded from this that there was no decrease in the arterial saturation but rather an increased saturation during tachycardia. The arterial oxygen saturation was not determined in the presence of the normal sinus rhythm and this conclusion is based on the assumption that the arterial saturation was normally 95 per cent. It is possible, however, that the arterial saturation normally may have been higher than 96.8 per cent, so that there may have been a slight decrease in the saturation. The anoxic anoxemia found in this case is also contrary to the conclusion

of Meakins that tachycardia without pulmonary congestion and edema does not produce a decrease in the oxygen saturation of the arterial blood. In a footnote to Table 2, Meakins<sup>2</sup> states that the "samples were taken from fifteen to twenty minutes after the end of the tachycardia in each instance." Under these circumstances, the oxygen saturation could have returned to normal in the interval between the end of the tachycardia and the taking of the sample. It hardly seems justifiable to draw such a sweeping conclusion from the figures reported in this table. The rapid return of the circulation to a relatively normal status is shown by the fact that the venous oxygen content was normal one hour after the end of the paroxysm.

The extremely low arterial carbon dioxide content during the attack was probably due to overventilation of the lungs and to slowing of the circulation so that the blood remained in the lung capillaries longer than normally. The  $p_{\text{H}}$  of the arterial blood would be interesting.

During the attack of tachycardia the oxygen capacity of the patient's blood corresponded to a hemoglobin of 114.3 per cent. One hour later this was 106.1 per cent and on subsequent occasions was found to have fallen to 101.4 per cent (April 7) and 85.5 per cent (June 16). This change may indicate that the patient responded to an increased demand for oxygen as a result of the series of attacks by a physiologic increase in the amount of circulating hemoglobin.

The patient was too ill to take a vital capacity test during the paroxysm, but one-half hour after the attack it was 39 per cent normal, while with a regular heart action it ranged from 64 to 68 per cent normal.

#### SUMMARY

A case of auricular paroxysmal tachycardia was studied from the point of view of the blood gases. The findings include:

1. Marked decrease of the arterial oxygen saturation without demonstrable pulmonary congestion to account for this.

2. Extremely low carbon dioxide content of the arterial blood during the paroxysm.

3. Very low oxygen saturation of the venous blood, part of which was attributable to the anoxic anoxemia, but the greater part was a true stagnant anoxemia due to slowing of the circulation. This stagnant anoxemia had entirely disappeared one hour after the end of the attack.

4. Greatly increased coefficient of utilization during the paroxysm, indicating a very slow circulation rate.

5. Decrease in vital capacity immediately following the paroxysm.

In addition, there appeared to be a close connection between an acute infection and the disturbance of the cardiac mechanism. It was also noted that during quinidin sulphate therapy ectopic beats which had been numerous and troublesome disappeared.

# OBSERVATIONS OF THE CARDIOVASCULAR SYSTEM IN THYROID DISEASE<sup>\*</sup>

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The importance of the cardiovascular signs and symptoms in thyroid disease has been known from the earliest writings on goiter Parry,<sup>1</sup> in 1786, recognized the seriousness of these manifestations, his first case presenting grave cardiac disorders resulting in death Since that time practically all authors have agreed that the outcome of any case is greatly influenced by the state of the circulation and its response to therapy Mobius,<sup>2</sup> in 1896, emphasized the importance of tachycardia, palpitation, forceful beating of the heart and arrhythmia in the syndrome of thyrotoxicosis, and stated that exophthalmic goiter patients suffer and die mainly because of cardiac changes Hirschfelder<sup>3</sup> reviewed the subject and gave the prevailing opinions regarding the cardiovascular findings and their treatment Forchheimer<sup>4</sup> directed therapeutic measures in thyroid disease toward the support of the circulation Kocher<sup>5</sup> and others believed that the surgeon should be guided by the cardiac condition in choosing the time and extent of operation

In a careful electrocardiographic study of fifty-one goiter patients, Krumbhaar<sup>6</sup> recorded the findings before and after surgical treatment His observations indicated that the effects of prolonged thyroid intoxication on the heart were progressive in nature Such patients developed high pulse pressure, hypertrophy, arrhythmias, heart block and changes in the T-wave It is also of interest to note that in his cases successful medical or surgical treatment resulted in the disappearance of some of these abnormal manifestations In one of his cases transient auricular fibrillation occurred Fahrenkamp<sup>7</sup> reports a case of thyrotoxicosis with paroxysms of auricular fibrillation of short duration, and auricular

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<sup>></sup> Read before the California State Medical Society, Yosemite Valley, May, 1922

1 Parry Collections from the Unpublished Writings of the late C H Parry, Underwood, London, 1825

2 Mobius Die Basedowsche Krankheit, Nothnagel's System, 22 1, 1896

3 Hirschfelder, A D Diseases of the Heart and Aorta, Philadelphia, J B Lippincott Co, 1910, pp 574-592

4 Forchheimer, F The Prophylaxis and Treatment of Internal Diseases, New York, D Appleton & Co, 1910, pp 465-468

5 Kocher, quoted by Hirschfelder, footnote 3

6 Krumbhaar, E B Electrocardiographic Observations in Toxic Goiter, Am J Med Sc 155 175-203, 1918

7 Fahrenkamp, K Vorubergehende komplette Herzunregelmassigkeiten unter dem Klinischen Bilde der Arrhythmia perpetua, Deutsch Arch f klin Med 117 1-12 1914

fibrillation has frequently been observed as a permanent condition in the later stages of the disease. Auricular flutter, paroxysmal tachycardia, extrasystoles and sinus arrhythmia have also been noted. Blackford and Willius<sup>8</sup> found auricular flutter associated with exophthalmic goiter in three out of a series of sixteen cases of auricular flutter. White and Aub,<sup>9</sup> in a careful electrocardiographic study, found auricular fibrillation in six out of forty-seven cases of hyperthyroidism. Three of these were of the paroxysmal type. Paroxysmal flutter occurred in one case. Goodpasture<sup>10</sup> has described an unusual type of myocardial regeneration in hyperthyroidism.

The syndrome known as "neurocirculatory asthemia" or "effort syndrome" has been confused with thyrotoxicosis. It has been shown by Addis and Kerr<sup>11</sup> and others<sup>12</sup> that this syndrome is as frequent in persons without any thyroid enlargement as in those with moderate or great enlargement.

The purpose of this paper is to report the cardiovascular condition of patients with thyroid disease entering the University of California Hospital for treatment during the past two years. In addition to the usual observations on the size of the heart, condition of the vascular system, pulse rate, blood pressure, pulse pressure and metabolic rates, a special effort has been made to study the types of irregularity revealed by means of electrocardiograms and polygraph tracings.

#### GENERAL CONSIDERATIONS

Of the 181 goiters studied, 123 were classified as adenomas and fifty-eight as hyperplasias. In reviewing the adenomas no attempt has been made to draw a sharp distinction between the toxic and nontoxic types. Approximately, half of these cases showed no signs of toxicity, and in a relatively small number the goiter produced pressure symptoms only. The average age of these patients was 46 years and a tumor was noted at the average age of 29 years, or seventeen years before appearing for treatment. Symptoms had been present on the average for eight and three tenths years. Females were affected 106 times and

8 Blackford, J. M., and Willius, F. A. Auricular Flutter, *Arch Int Med* **21** 147-165 (Jan.) 1918.

9 White, P. D., and Aub, J. C. The Electrocardiogram in Thyroid Disease, *Arch Int Med* **22** 766-769 (Dec.) 1918.

10 Goodpasture, E. W. Myocardial Necrosis in Hyperthyroidism. *J. A. M. A.* **76** 1545 (June 4) 1921.

11 Addis, T., and Kerr, W. J. The Relative Frequency in Recruits with and Without Thyroid Enlargement of Certain Signs and Symptoms Which Occur in Neurocirculatory Asthenia. *Arch Int Med* **23** 316-333 (March) 1919.

12 Norris, G. W., and Landis, H. R. M. Diseases of the Chest and the Principles of Physical Diagnosis, Philadelphia, W. B. Saunders Company, 1920 pp. 692-695.

males seventeen times Cardiovascular symptoms were more or less marked in 44 per cent of the cases Rapid and forceful beating of the heart and "palpitation" were the symptoms usually complained of, although vasomotor disturbances, irregularities of the heart, dyspnea and breathlessness were frequently noted Pain in the region of the heart and anginal attacks were rare Central nervous system symptoms, including nervousness, tremors, astasia abasia and emotional instability, were described in fifty-eight cases Gastro-intestinal symptoms, usually diarrhea, or diarrhea alternating with constipation, were complained of in only four cases There was marked progressive loss of weight in

TABLE 1—GENERAL FINDINGS

Type of Goiter	No of Cases	Sex	Average Age, Years	Average Age Tumor Noted	Average Duration of Symptoms	Number with Eye Signs	Number with C N S Symp-toms	Number with Gastro Intes tinal Symp-toms	Marked Loss of Weight	Average Basal Metabo lism, per Cent	Number of Deaths
Adenomas toxic and nontoxic	123	M 17 F 106	41 38	29 2 years	8 3 years	1 slight 6 doubtful	58	4	8	30 2 + (all forms) 47 + (toxic only)	2
Hyper-plasias	58	M 15 F 43	36 4	33 9 years	3 months	44 5 doubtful	56	17	38	58 7 +	7

TABLE 2—GENERAL CARDIOVASCULAR FINDINGS

Type of Goiter	No of Cases	Cardiac Symp-toms	Per Cent with Cardiac Symp-toms	Average Pulse Rate	Average Blood Pressure		Average Pulse Pressure	Number with Cardiac Enlarge-ment	Number with Mur-murs	Number with Over Thyroid or Tum-oral Arteries	Number with Signs of Decom-pen-sation
Adenomas toxic and nontoxic	123	54	44	85 (95 in toxic cases)	Sys tolic 133	Dias tolic 78	55	41	43	3	3
Hyperplasias	58	53	91	107	141	71	70	43	46	33	15*

\* Three of these cases presented unusual and marked systolic pulsations of the veins of the forearms and hands

eight cases and a gain in two cases In no case was there marked exophthalmos When the eye changes were noted, usually only one or two of the minor signs were described The average basal metabolic rate, when determined, was 30 2 per cent above the theoretic normal, but when the nontoxic cases were excluded, the average rate was 47 per cent above the theoretic normal There were two deaths

Of the fifty-eight cases with hyperplasia, forty-four presented exophthalmos and other eye signs, and in five others these eye signs were slight or doubtful The average age was 36 4 years and the tumor was observed at the average age of 33 9 years, or two and five-tenths years before entering the hospital for treatment Females were affected forty-three times and males fifteen times Symptoms had been present

for a relatively brief period. In about one-third of the cases the tumor was noticed before the onset of symptoms, in about one-third, the appearance of the symptoms preceded the discovery of the tumor and in the remainder, the symptoms and tumor appeared at the same time. The average duration of symptoms was about three months. Cardiovascular symptoms were complained of in 91 per cent of the cases. "Palpitation" and rapid, forceful beating of the heart were usually present, irregularities, dyspnea, breathlessness and vasomotor disturbances were common. Fifteen cases presented signs of decompensation. Central nervous system symptoms were present in fifty-six cases and were more pronounced than with the adenomas. Gastro-intestinal symptoms such as diarrhea and vomiting were complained of in seventeen cases. There was a definite loss of weight in thirty-eight cases. The basal metabolic rate averaged 58.7 per cent above the theoretic normal. There were seven deaths.

#### SPECIAL CONSIDERATION OF CARDIOVASCULAR SYSTEM

*Symptoms*—A brief statement of the cardiovascular symptoms is given above. It is the prevailing opinion that the hyperplastic goiter causes more profound changes in the circulatory system than is found in association with toxic adenomas. Our observations suggest, however, that, so far as the heart is concerned, the disturbances are practically the same in both groups. Where differences occurred, they seemed to be due mainly to the degree of toxicity. The vascular system, however, showed more pronounced changes in the hyperplastic group than in the group of adenomas. Among the earliest symptoms were tachycardia and a consciousness of the heart beat. Many patients complained of attacks of "palpitation." These spells, which were more frequent later in the disease, probably represent paroxysmal attacks of auricular fibrillation or flutter. Throbbing of the vessels in the neck and periphery, pulsation in the thyroid and a heaving precordium were usually marked in severe cases. Sleep was frequently interfered with because of these sensations and such patients preferred to lie on the right side. Dyspnea and breathlessness on exertion, and in the later stages cough, progressive edema, cyanosis and other signs of decompensation were observed where proper treatment had not been instituted. Goiters producing pressure symptoms were relatively infrequent causes of cardiovascular disturbances, as compared with the overacting glands.

*Physical Signs*—Inspection in the early cases revealed very little aside from a forceful apex impulse in the usual position, slightly increased carotid pulsations and flushing of the face and neck. As the disease advanced, the apex impulse became more forceful with a diffuse heaving of the precordium. The apex impulse was then displaced to the

left and, in later stages, downward. The carotid arteries and peripheral vessels showed increased pulsations, and capillary pulsation was frequently noted, especially in the hyperplastic cases. When the myocardium began to fail, the venous pressure rose, the veins stood out and they occasionally showed unusual systolic pulsations extending to the lower arm and hand (noted in three of our cases). When decompensation began, the usual signs appeared such as pulsating liver, systolic venous pulse in the neck, edema of the lungs and edema of the legs advancing to anasarca. During the stage of decompensation, the heart was frequently irregular and no sign of an *A*-wave could be found in records from the jugular vein.

On palpation the apex impulse was usually forceful and showed no displacement in early cases, but as the condition advanced, the impulse became more marked and diffuse, and it moved to the left and downward. A systolic or presystolic thrill at the apex, or a systolic thrill at the pulmonic area was noted in a few cases. A distinct shock was felt at the pulmonic area, accompanying the second sound. A systolic thrill was frequently felt over the thyroid vessels in hyperplastic glands, rarely in adenomas. The pulse was usually soft and often times dichrotic. A water-hammer pulse was common in the hyperplasias. The rate was quickened in toxic cases, being 93 in the toxic adenomas and 107 in the hyperplasias in our series. In the early stages the pulse was generally regular, although a sinus arrhythmia of the respiratory type was frequently observed. Later, many cases showed the more unusual types of irregularities, and in the terminal stages they were very commonly observed.

By percussion the heart was found to be gradually enlarged to the left and downward, there was a well defined increase in dulness in the third and fourth left interspaces, as is seen in organic mitral disease, and later the dulness was increased to the right. Enlargement, usually to the left, was noted in forty-one adenomas and in forty-three hyperplasias. In the absence of thymic enlargement or a substernal extension of the thyroid, the substernal dulness was found to be increased, due to the dilatation of the great vessels.

Auscultation revealed the signs of an overacting heart in toxic cases. The sounds were quickened, ringing and loud, giving an impression of hurried ineffectiveness. As the condition advanced, a soft systolic murmur was usually heard at the apex and a short rough, systolic murmur was heard at the pulmonic area. Later a loud systolic murmur was frequently heard all over the precordium and was transmitted to the vessels of the neck, with a bruit over the thyroid vessels and gland. A definite bruit was noted over the gland in thirty-three cases of hyperplastic thyroids and in only three of the cases with adenomas. In the advanced stages of myocardial failure a diastolic

murmur was occasionally heard at the pulmonic area or a soft systolic murmur appeared over the tricuspid area. Murmurs were noted in our series in forty-three cases of adenomas and in forty-six cases of hyperplasia.

An unusually large number of cardiac irregularities were observed. Of sinus arrhythmia we have no accurate data as its finding was considered of little significance. It was frequently observed and possibly should be studied further. Extrasystoles were observed in only nine cases and in two of these it is probable that an unrecognized auricular fibrillation was present. Auricular fibrillation was observed in twenty-nine cases, occurring in nine cases with adenomas and twenty cases with hyperplasia. In fifteen of the twenty-nine cases, the fibrillation was paroxysmal in type and in several cases many attacks were observed. Figure 1 shows the frequency and duration of such attacks in one of our cases. In eight cases auricular fibrillation alternated with auricular flutter, and in two cases auricular flutter was observed alone. Paroxysmal auricular tachycardia with a rate of 190 occurred in one case (Table 3).

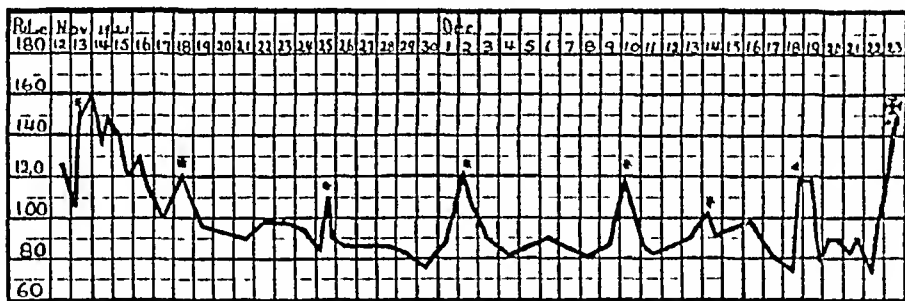


Fig 1—Case 9102. Paroxysmal auricular fibrillation. Paroxysms indicated by asterisks. Death occurred one and one-half hours after operation in an attack of auricular fibrillation which began during the operation. All attacks responded to digitalis in moderate doses except the one preceding death.

These observations on the frequency of cardiac irregularities have suggested that many of the attacks of "palpitation" which patients describe are due to the disturbance of the normal mechanism of the heart beat by the inception of one of these unusual rhythms. Such attacks frequently came on suddenly and usually lasted only a short time. They were accompanied by a sense of fullness in the chest, a disagreeable, rapid, forceful action of the heart, flushing of the face and neck, and breathlessness. The termination was usually abrupt. On questioning patients who were seen during attacks of auricular fibrillation or flutter, it was found that their sensations were the same as those experienced during the previous spells of so-called palpitation. In our opinion, this shows pretty clearly that what they call palpitation is really the result of serious auricular fibrillation or flutter. We feel sure that this has not been sufficiently recognized in the past.



*Roentgen-ray* studies on the toxic cases generally showed the heart to be enlarged to the left with widening in the region of the conus and left auricle—the so-called “mitral type” In some cases, particularly of the hyperplastic group, the heart was of the “aortic type” with the great-vessel shadow definitely increased

*Blood pressure* determinations showed in the adenomas an average of 133 mm mercury (systolic), 78 mm mercury (diastolic) and a pulse pressure of 55 mm mercury, while in the hyperplasias the average

TABLE 3—CARDIAC IRRREGULARITIES

Type of Goiter	No of Cases	Auricular Fibrillation	Auricular Flutter	Paroxysmal Tachycardia	Extra systoles	Sinus Arrhythmia
Adenomas toxic and nontoxic	123	9 (4 paroxysmal) (2 alternating with auricular flutter)	3 and 1 probable (2 alternating with auricular fibrillation)	1 (rate 190)	6 including 2 cases of probable auricular fibrillation	Frequent, no exact data
Hyper- plasias	58	20 (11 paroxysmal) (6 alternating with auricular flutter)	4 and 2 probable (all alternating with auricular fibrillation)	0	3	Frequent no exact data
Totals	181	29	7 3 probable	1	7 2 doubtful	Frequent

TABLE 4—BLOOD PRESSURE IN TOXIC ADENOMAS

Case Number	Before Operation	After Operation
11447	215/107	110/80 6 mos later, 170/90
12349	190/100	110/70
12778	160/80	128/75
13480	150/80	121/60
11765	188/100	133/70
13828	190/95	130/70
13451	180/110	145/90
8541	190/100	160/80
10777	218/142	160/100

TABLE 5—BLOOD PRESSURE IN THE HYPERPLASIAS

Case Number	Before Operation	After Operation
12976	152/86	122/82
11586	145/65	138/45
10444	140/90	128/75

was 141 mm mercury (systolic) and 71 mm mercury (diastolic) with a pulse pressure of 70 mm mercury In several cases in which the systolic and diastolic pressures were high before operation, a marked fall was observed following surgical treatment Some of the more striking examples are shown in Tables 4 and 5 In one patient with a hyperplastic goiter who had a blood pressure of 200/100 on admission, there was a fall to 178/65 after medical treatment

*Venous Pressures and Pulsations*—No attempt was made to measure accurately the venous pressures, but in advanced cases the pressure in

the veins was definitely increased. In three cases we observed pulsating peripheral veins in the arms and hands, which cleared up after treatment.

*Electrocardiographic* and *polygraphic* tracings were made in most of the cases showing unusual irregularities and in some of the uncomplicated cases. Twenty-five cases were studied at intervals while in the hospital. In addition to the changes in rhythm noted, there were certain variations in the auricular complex which were frequently observed in more severe cases. The *P*-waves were widened and increased in amplitude, frequently slightly notched in Lead I and having a diphasic character in Lead III. These features were noted in ten out of fourteen cases with regular rhythm. The *P*-*R* interval was five

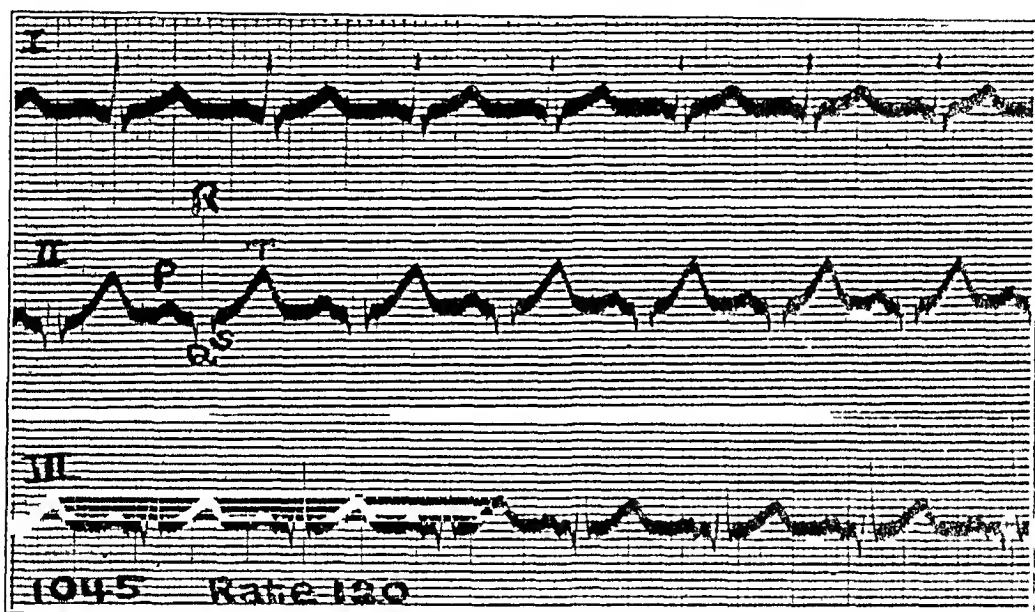


Fig 2—Electrocardiogram 1045. Marked hyperplasia. Rate 120. Notching of "P" waves in Lead III. Prominent "T" waves, all leads. Died after operation of marked-thyrotoxicosis and focal necrosis of liver and pancreas. (For this and all succeeding electrocardiograms, the time marker records twenty-fifths of a second. The galvanometer string is so standardized that deflections of one centimeter represent one millivolt.)

twenty-fifths second in three cases and there was an arborization block in one case. Bundle branch lesions were not observed. Right hypertrophy was shown in two cases and left hypertrophy in three cases. The *T*-wave, when flattened or inverted in Leads I and II, has been found to indicate a bad prognosis in accordance with the findings of Krumbhaar. In our series there were six such cases, all showing advanced myocardial disease, and as was to be expected, two or 33 per cent of the patients died. Examples of the various types of irregularities are shown in Figures 2 to 5.

*Diagnosis*—The diagnosis of the types of goiter studied were made on the clinical signs and symptoms combined with pathologic findings at operation and necropsy. The cardiac symptoms and signs were usually obvious, although careful observation and instrumental means were frequently necessary to differentiate the irregularities encountered.

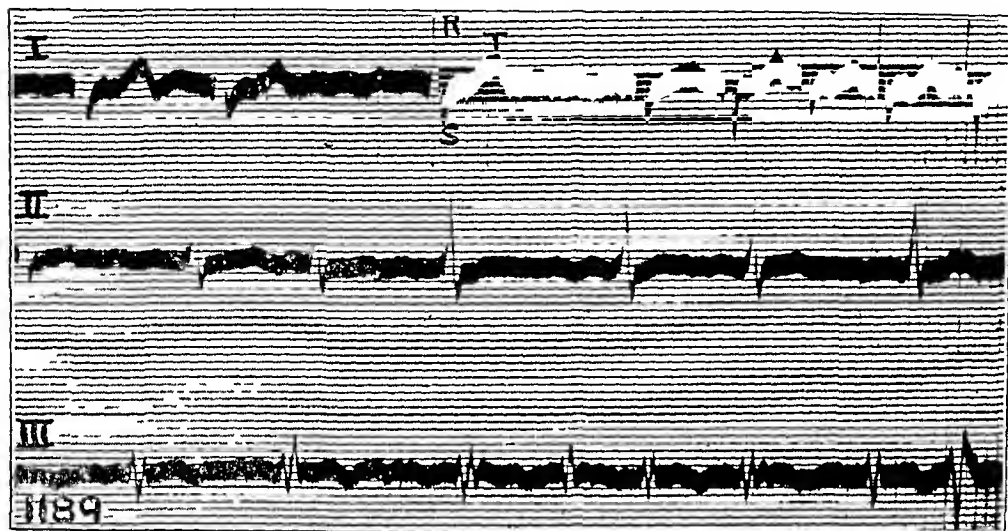


Fig 3—Electrocardiogram 1189. Marked hyperplasia. Paroxysmal auricular fibrillation. Slight right hypertrophy. Inverted "T" waves in Lead III.

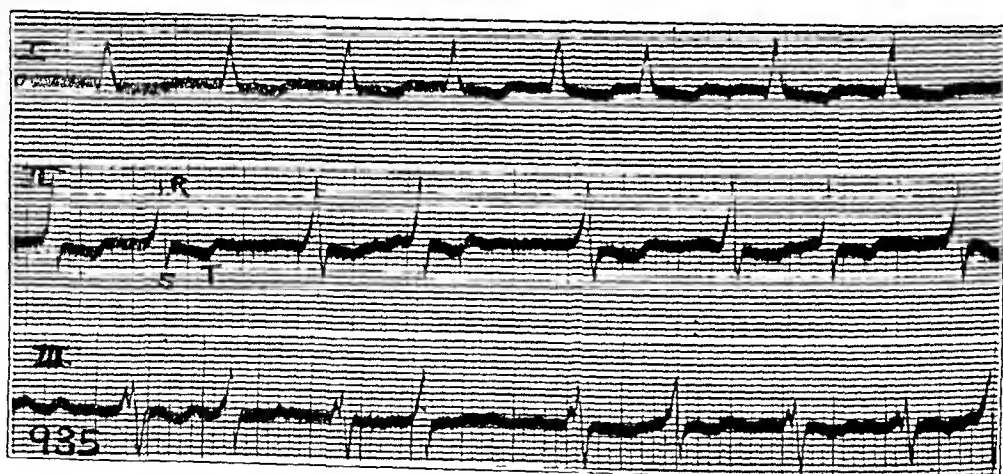


Fig 4—Electrocardiogram 935. Marked hyperplasia. Advanced myocardial changes with decompensation, peripheral venous pulsations. Auricular fibrillation. Inverted "T" waves in all leads. "Q-S" interval two twenty-fifths of a second. Radium treatment. Living after six months.

*Treatment*—No preliminary treatment was given in the nontoxic or moderately toxic adenomas previous to operation. The patients with more advanced toxic adenomas, with signs of cardiac failure, and most of the patients with hyperplasias were given preliminary medical treatment or received medical treatment alone. Mental and physical

rest was insisted on. Bromids or quinin hydrobromate were given when indicated. Ice bags were used over the thyroid gland and heart in the more toxic cases with considerable relief from distressing symptoms. Digitalis, in the form of the tincture, was used when indicated, under careful supervision. In moderate doses the drug produced excellent results and was very useful in controlling and, possibly, in preventing attacks of abnormal cardiac rhythms, particularly auricular fibrillation. One patient died during operation, from the effects of toxic procain used as a local anesthetic. Another death occurred from auricular fibrillation with marked signs of thyrotoxicosis developing two days after operation. Quinidin sulphate seemed to have a beneficial effect in controlling attacks of auricular fibrillation in one case, although of no benefit in several others. Cardiac decompensa-

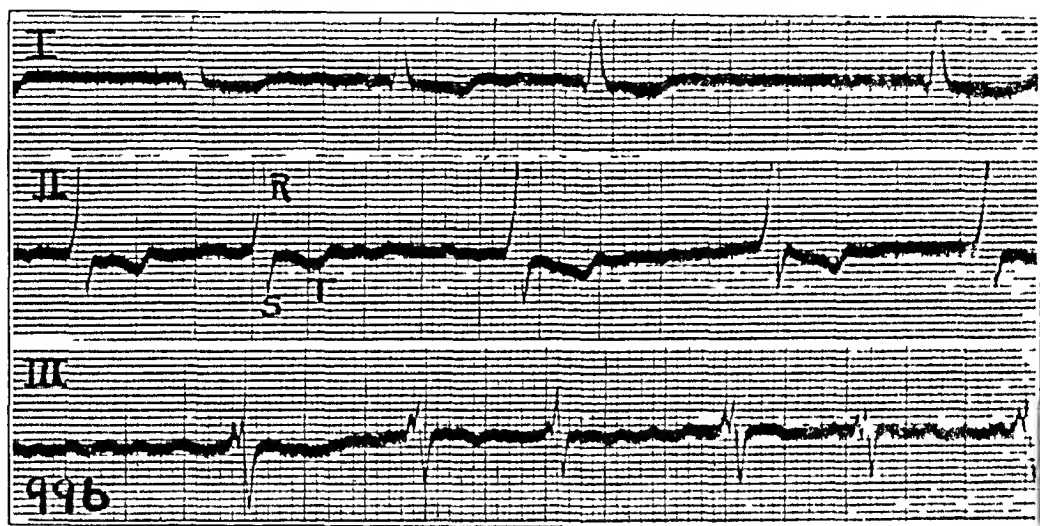


Fig 5—Electrocardiogram 996 Same as 935 after digitalis therapy. Rate reduced from 135 to 75 per minute.

tion was treated by the approved methods, although excessive purgation was very exhausting in some cases. Roentgen-ray treatment was used in many cases of hyperplasia before operation and in a few cases it was the only local treatment employed. Radium emanations in bare tubes of from 6 to 10 mc were inserted into some of the more serious hyperplastic goiters with marked improvement. (These cases are being reported elsewhere by Dr W I Terry.) Various methods of surgical treatment were employed, including ligation, enucleation of adenoma, partial lobectomy, bilateral subtotal lobectomy, etc.

One of the most striking observations made in this series of cases has been the degree of cardiac relief noted by the patient after removal of an overacting thyroid gland.

*Prognosis*—In our series it has been demonstrated that the condition of the heart generally determined the outcome of the case. Deaths

from other causes, except marked increase of toxicity following operation in severe cases, were rare. Electrocardiographic demonstration of flattened or inverted *T*-waves in Leads I and II have indicated an unfavorable outcome. Heart block and disorders of the cardiac rhythm have been noted in the more severe cases. Signs of decompensation and advancing edema have indicated prolonged medical treatment or radiotherapy. Embolism and coronary disease were rare. Focal necroses of the liver and pancreas followed operation in one case and caused the death of the patient.

*Mortality*—In our series there were nine deaths, seven occurring in cases with hyperplasia, one with a mixed gland and one with an adenoma of the plunging type. The findings in these cases have been briefly summarized below.

#### REPORT OF CASES

**CASE 1 (8505)**—Female, aged 46. Symptoms and tumor for eight years with slight pressure on trachea, enlarged heart, blowing systolic murmur at mitral and pulmonic areas, loud bruit and thrill over gland, pulse, 130, blood pressure 120/80 mm mercury, basal metabolism 70 per cent plus. She was given preliminary medical treatment, and radium, 10 mc, was inserted into the gland with slight improvement. Later bilateral subtotal lobectomy was done with only slight improvement. One month after operation she had a brief attack of auricular fibrillation. Basal metabolism, 66 per cent plus. Four months after operation basal metabolism was 58 per cent plus. Then nine exposures to the roentgen-ray in another city were followed by marked thyrotoxicosis, pulse 200, coma, delirium and death. At the necropsy a large amount of hyperplastic gland was found surrounding the trachea and extending beneath the manubrium.

*Diagnosis*—Recurrent hyperplasia with marked thyrotoxicosis.

**CASE 2 (12563 and 13060)**—Male, aged 39. Symptoms present three years, very marked during past five months, tumor noted three weeks, heart enlarged, pulse, 120, blood pressure, 120/64, slight eye signs, marked bruit, basal metabolism, 79 per cent. He was given medical treatment and radium 6.5 mc, was inserted into the gland. Very slight improvement. Two months later, a bilateral partial lobectomy was done. Thirteen days after operation there developed progressive jaundice, coma, convulsions, dyspnea and cyanosis. Urobilin was present in the urine (no leucin or tyrosin) and the man died in coma. The necropsy showed marked acute focal degeneration of the liver, focal necrosis of pancreas, hyperplasia of thymus.

*Diagnosis*—Hyperplasia with marked thyrotoxicosis and liver degeneration.

**CASE 3 (13360)**—Female, aged 31. Tumor present five years, symptoms manifested two years with palpitation and diarrhea, heart slightly enlarged with systolic murmur at mitral area and diastolic murmur at pulmonic area. She entered the hospital with a pulse of 180, blood pressure, 160/90, gangrene of right arm. Amputation. Pulse rose to 200, temperature increased from 38 to 42 C, and the patient died with cardiac failure and toxemia. The necropsy showed thrombosis of right subclavian artery. No thrombi found in heart. Right ventricle dilated.

*Diagnosis*—Hyperplasia with cardiac dilatation and arterial thrombosis.

**CASE 4 (10751)**—Female, aged 39. Symptoms present for many years, tumor noted for eighteen months, with decompensation for eighteen months with anasarca, marked hypertrophy and dilatation of heart, systolic murmurs at mitral and pulmonic areas, auriculoventricular block (partial), pulse 90, blood pressure 140/60, marked eye signs, basal metabolism, 56 per cent plus. She

had had six roentgen-ray treatments fifteen months previously. She was given medical treatment, and radium, 76 mc, was inserted into the gland, followed by three roentgen-ray treatments. Patient died three months later of decompensated heart. Necropsy (limited to abdominal organs) showed cirrhosis of liver, diffuse brown atrophy, infarct in right kidney.

*Diagnosis*—Hyperplasia with advanced myocardial disease and cirrhosis of liver.

CASE 5 (8027)—Female, aged 30. Symptoms and tumor present fifteen months, heart enlarged, loud systolic murmur all over precordium, pulse, 130, blood pressure, 140/70, marked bruit over gland, marked eye signs. Preliminary medical treatment with extraction of abscessed teeth and tonsillectomy with slight improvement. Operation. Bilateral partial lobectomy. Patient died during operation from probable effects of toxic procain. She had been given 18 cc of tincture of digitalis during the four days previous to operation.

*Diagnosis*—Hyperplasia. Anesthetic death.

CASE 6 (7630)—Female, aged 35. Extreme symptoms present for eight months with attacks of palpitation resembling auricular fibrillation, tumor noted eight months, heart enlarged, pulse, 108, blood pressure, 135/70, marked eye signs. Radium, 10 mc, was inserted into gland. One month later patient was improved and a bilateral partial lobectomy was done. Pulse was irregular, with auricular fibrillation before operation, and patient received 20 cc tincture of digitalis during four days previous to operation. Digitalis was stopped after operation. Two days later fibrillation returned with marked thyrotoxicosis, the patient rapidly failed and died. Digitalis probably should have been continued after operation.

*Diagnosis*—Hyperplasia with myocardial changes and paroxysmal auricular fibrillation.

CASE 7 (9120)—Female, aged 52. Tumor noted fifteen years, symptoms manifested only three weeks, with marked palpitation in paroxysms, and dyspnea. There had been pressure symptoms for three years. Heart was markedly enlarged, with heaving precordium, pulse, 120, systolic blood pressure, 190, diastolic sound heard to zero, marked capillary pulse, marked bruit and eye signs. Seven paroxysms of auricular fibrillation of brief duration were observed before operation. There were attacks of anginal pain. Preliminary intermittent digitalis therapy was given. The goiter was "stolen." Auricular fibrillation returned during operation and continued until death an hour and a half after operation (Fig 1). Pathologic section of gland showed colloid goiter with evidence of some hyperplasia. Adenomas also present.

*Diagnosis*—Mixed type of goiter with marked myocardial changes and paroxysmal auricular fibrillation. Angina pectoris.

CASE 8 (5486)—Female, aged 41. Tumor noted twenty-six years, previous operation thirteen years ago. Tumor returned six years ago, general symptoms manifested five years with pressure symptoms. Heart enlarged, arch widened with probable substernal thyroid, systolic murmur over base transmitted to carotids, and thyroid arteries. Many paroxysms of auricular fibrillation alternating with auricular flutter, flattened T-waves in Lead I by electrocardiograph. Pulse 100, blood pressure, 130/60 (variable), no eye signs, marked loss of weight, diarrhea, basal metabolism, 76 per cent plus. Preliminary medical treatment and six roentgen-ray treatments were given. Patient died two hours after operation with auricular fibrillation. Sections of the gland showed multiple adenomas with hyperplastic and degenerative changes. The sections also suggested the presence of tuberculosis, although no signs of that disease were found elsewhere.

*Diagnosis*—Mixed type of goiter with advanced myocardial disease, auricular fibrillation and flutter.

CASE 9 (13038)—Male, aged 76. Slight symptoms noted for three years with recent severe pressure symptoms. Tumor noted one and one-half years

Heart enlarged to left, no murmurs, pulse, 100, blood pressure, 135/75. Plunging type of goiter. Operation difficult. Patient died one and one-half hours after operation from local hemorrhage and pressure on the trachea.

*Diagnosis*—Toxic degenerating adenomas with pressure symptoms. Post-operative hemorrhage with tracheal pressure.

#### CONCLUSIONS

1 The cardiovascular changes in thyroid disease are progressive, and in the most severe cases dominate the clinical picture.

2 The cardiac signs and symptoms in toxic adenomas and hyperplasias differ only with the degree of toxicity. The vascular changes are more marked in the cases of hyperplastic goiter.

3 Cardiac irregularities are more common than is generally recognized. Auricular fibrillation or auricular flutter, usually paroxysmal in type, occurred in about one-third of all toxic cases. We believe that such paroxysmal attacks explain the periods of palpitation which are described by a large percentage of patients.

4 The prognosis depends in a large measure on the condition of the circulation. If surgical treatment is to be carried out, the "time and extent of the operation should be governed by the circulatory condition."

5 Treatment of the thyroid heart depends on the stage of the disease. In all cases every measure should be employed to relieve the myocardium. Rest is essential. Sedative drugs are of some value. Elimination should be kept up. Digitalis is of great value in controlling auricular fibrillation and may be of value in preventing paroxysmal attacks. The amount required in controlling auricular fibrillation is usually less than in ordinary cardiac cases. It should be continued over long periods. Decompensation should be treated as in other myocardial cases.

6 The electrocardiogram is of value in recognizing myocardial changes, in differentiating the types of irregularities and in prognosis.

# A CASE OF RHEUMATIC FEVER WITH CEREBRAL SYMPTOMS SIMULATING ENCEPHALITIS LETHARGICA

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*History*—Mrs J F, aged 54, had a sharp attack of tonsillitis, Feb 14, 1922, the temperature rising to 102.4 F, and culture showing *Streptococcus viridans*. Two days later she began to have joint pain, and large, elevated, red and tender nodes on the skin of the neck, and over the shins, typically an erythema nodosum.

*Past History*—She had had typhoid fever, a severe case, at the age of 10, bronchopneumonia at 19, and frequent attacks of tonsillitis, headaches of a migrainal type, hemicranial in nature with occasional hemianopsia.

She first consulted me in November, 1921, complaining of numbness and tingling in the arms, and legs, particularly in the left arm. One month before there was temporary loss of power of about one hour's duration. She was also confused mentally at this time. Her menstrual history began at 16, and was uneventful. Her marital history showed numerous miscarriages. She has one living, healthy child.

*Physical Examination*—Patient was a slight, frail woman, with slightly coated tongue, a good deal of bridge work on the molar teeth, but no definite evidence of infection. Tonsils were small, buried, and contained cheesy particles. Pupils were equal, reacted to light and accommodation. Arteries of the retina were small and tortuous. Blood pressure was elevated, systolic, 204, diastolic, 108. Heart. Some left ventricular enlargement, with a systolic murmur at apex, transmitted to the left, and a sharply accentuated second aortic sound, and a second murmur over the aorta transmitted to the vessels of the neck. The urine contained a very faint trace of albumin, but no casts, was of low specific gravity (1.010), but on the Mosenthal test (night specimen), showed that she still had ability to concentrate, and water produced a diuretic effect.

*Blood chemistry* was entirely normal. Blood Wassermann negative. Phenol-sulphonaphthalein, normal. A lumbar puncture was made with the idea of possible central nervous lesion, but the spinal fluid was completely normal. Wassermann, Lange's colloidal gold curve, butyric, and cells completely negative.

*Diagnosis*—Cerebral arteriosclerosis, and chronic endocarditis.

*Treatment*—She was put on proper diet, and made a symptomatic recovery within a few weeks.

*Clinical Course*—Seven days following her acute tonsillitis in February, 1922, she began to show meningeal symptoms. Slight diplopia with left internal rectus muscle weakness, and an Oppenheim reaction were present, with doubtful Babinski, though no Kernig, and only very slight stiffness of the neck. Patellar reflexes were obtained. The areas of erythema nodosum were more numerous and painful. She had a slight dry, hacking cough, and an occasional fine subcrepitant r le in the right scapular region. Roentgenogram of lungs was negative. Her temperature was 103 F, respiration, 30, pulse, 116. Her leukocytes numbered 18,000, polymorphonuclears, 87 per cent. Lumbar puncture revealed a fluid showing only two cells with a faintly positive butyric acid test.

The following day her meningeal symptoms were more marked. The patient became restless, and wildly irrational. Her neck was stiff. The left internal rectus muscle weakness was more marked, as was the Babinski, and the Oppenheim



reaction was more definite. Still no Kernig present. There were many fresh areas of erythema nodosum on both shins. Eyegrounds were negative except for vascular changes noted in November.

The following day the patient was semistuporous, the face showing the Parkinsonian masklike expression. Rigidity of neck continued. Babinski still present. Patellar reflex not obtainable. Blood culture and spinal fluid completely negative. At times there were severe pains running down the arms, of transitory duration, suggesting posterior root pain. At this time the patient presented an appearance fairly characteristic of encephalitis lethargica, but as it occurred in the course of rheumatic fever, and with a negative spinal fluid it was considered to be cerebral edema, with pressure on the optic thalami.

Owing to the uncertain diagnosis I requested Dr. Samuel Lambert to see her in consultation at 3 p. m. At 2 p. m. the patient's respiration had become difficult, she was completely comatose, recognizing no one. The nurse and family were much alarmed. When we saw her at 3 p. m., she was bright, and recognized everyone readily, talked without discomfort, though the Babinski and stiff neck persisted. February 25 slight facial weakness, and slight choreiform movements appeared. February 28, though her temperature was running a lower curve, the patient again became rather stupid, and did not cooperate well. She had slept most of the time for the past twenty-four hours. On March 1 she was seen in consultation by Dr. Foster Kennedy, who concurred in the diagnosis of encephalitis, not epidemic in nature. He also believed that her failure to cooperate and answer was due to an aphasia. Eyegrounds still remained normal.

On March 4 the aphasia was less marked and better cooperation could be obtained. She had no agraphia. March 12, there was slight diplopia, the margin of the right disk was slightly indistinct, and patellar reflexes had returned. By April 1 she had made a complete recovery. The cardiac signs remained unchanged throughout her illness.

#### CONCLUSION

This case is presented because of the particular interest attached to a diagnosis of a disease simulating encephalitis lethargica, but in all probability not etiologically related to it. The symptoms are believed to have been due to a localized edema of the brain, first in the thalamic region or falx, causing, by pressure symptoms typical of true epidemic encephalitis, and an aphasia due to a small localized edema in the speech area. The sudden remission of symptoms February 2, was due to the sudden disappearance of the edema, with consequent improvement of symptoms.<sup>1</sup>

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<sup>1</sup> Dr. Foster Kennedy has reported three cases of similar nature, *Arch Neurol & Psychiat* 7 53 (Jan) 1922.

# GRAVIMETRIC ESTIMATION OF PHOSPHATES OF THE BLOOD

PHOSPHATES IN NEPHRITIS

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The methods at present employed for the estimation of blood phosphates involve the use of colorimetric or nephelometric determinations. Embden<sup>1</sup> recently described a technic for the gravimetric estimation of small amounts (from 1 to 4 mg.) of phosphoric acid in muscle. It seemed desirable to attempt to apply this method to the estimation of phosphates in whole blood. This method proved in use to be satisfactory, and it was then decided to apply it to the study of the phosphates in the blood in nephritis. The excretion of acid phosphate by the kidney is one of the chief lines of defence of the body against an abnormal accumulation of acid in the blood; moreover, the buffer action of the phosphates may help to keep the reaction of the blood within physiologic limits. In the latter mechanism it is obvious that only the inorganic phosphate in the blood can be concerned. It has already been stated by Marriott and Haessler<sup>2</sup> that the inorganic phosphates of the blood are increased in severe nephritis, but the relationship between inorganic and total phosphates in pathologic conditions has not been investigated so completely. It was, therefore, with the object of obtaining data on this point that the present investigation was undertaken.

## EXPERIMENTAL

The method of Embden<sup>1</sup> for the estimation of phosphoric acid depends on its precipitation in the form of the complex alkaloidal salt strychnin phosphomolybdate. The weight of the precipitate obtained is equal to the weight of phosphoric acid present, multiplied by 28.24. A method essentially the same as this in principle has been applied by Bloom to the nephelometric estimation of phosphoric acid in blood but it will be seen from the magnitude of the above factor that from a relatively small quantity of blood, a sufficient precipitate can be obtained to weigh accurately. It seemed, therefore, reasonable to expect that the additional accuracy to be obtained by this gravimetric method would more than counterbalance the extra time expended in carrying it out.

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\* From the Department of Therapeutics, University of Edinburgh.

1 Embden, *Ztschr. f. Physiol. Chem.* **113**, 138, 1921.

2 Marriott and Haessler, *J. Biol. Chem.* **32**, 241, 1917.

*Technic*—The technic of the method is as follows

For the estimation of inorganic phosphate 5 cc of whole blood were employed. The blood was measured into a 50 cc flask and diluted to about 25 cc with warm water at a temperature of from 35 to 40 C. The diluted blood was allowed to stand fifteen minutes with frequent shaking to insure complete laking and 10 cc of an 11 per cent solution of trichloroacetic acid was then added. The contents of the flask were well mixed and diluted to the mark with water. After mixing and standing for a few minutes, the solution was filtered through a dry phosphate free filter paper. Twenty-five cubic centimeters of the water-clear filtrate was taken for the estimation, and sufficient water added to make the total volume, after the addition of the precipitating reagent, 75 cc. The further steps will be described in connection with the estimation of total phosphates.

For the determination of total phosphates, 25 cc of whole blood were measured into a 25 cc flask and laked by dilution with warm water, as in the case of the inorganic phosphates. It was then made up to the mark and well mixed. Five cubic centimeters of this diluted blood was measured into a large silica test tube which had previously been cleaned by boiling strong sulphuric acid in it for twenty minutes. There was then added 2 cc of a

TABLE 1—VALUE OF THE USE OF CANE SUGAR TO ASSIST COMBUSTION  
IN TOTAL PHOSPHATE ESTIMATION

Experiment	No Cane Sugar Used, Mg $H_3PO_4$ per 100 C c	Cane Sugar Added, Mg $H_3PO_4$ per 100 C c
1	123.9	119.6
2	125.3	112.6
3	139.5	128.8
4	134.5	133.1
5	127.4	124.6
6	118.2	128.8
7	133.1	125.3
8	79.3	69.4

mixture of equal parts of strong sulphuric and nitric acids and a few glass beads to prevent bumping. The combustion of the organic substances was carried out carefully in a manner which was virtually identical with that described by Bloor<sup>3</sup>.

The mixture was first raised to boiling and the flame was then turned down until only a slow bubbling took place. When most of the water had been driven off a small glass funnel was inserted into the mouth of the tube to eliminate all possibility of loss of contents by spurling and also to prevent the nitric acid from boiling off too quickly. Heating at this rate was continued until red fumes ceased to come off. The flame was then increased and strong heating was continued for from eight to ten minutes. In many cases the contents of the tube after this treatment retained still a yellowish tinge. If this were the case, a drop of strong nitric acid was added and the heating continued for one or two minutes. By this treatment complete clearing was obtained.

Bloor<sup>3</sup> recommends the addition at this stage of one or more drops of 1 per cent cane sugar solution and subsequent reheating until the brown color caused by the addition of the cane sugar disappears. He

states that unless this precaution is observed, low results for phosphates are obtained. This point has been investigated and the results of analyses carried out with and without the use of cane sugar to assist the combustion are shown in Table 1. From these figures it appears that the results obtained without the use of cane sugar are, if anything, higher, but the difference is not very significant. The cane sugar, therefore, was not employed in the majority of the analyses recorded herein.

After completion of the combustion and cooling, the contents of the tube were thoroughly washed out with water into a 250 cc Erlenmeyer flask. Three drops of bromophenol blue were added to the solution and the solution was made alkaline with ammonia, dilute sulphuric acid was then added until the indicator just changed color. After thorough cooling, the solution was treated with the precipitating reagent, the total volume being made up to 75 cc. The further technic is the same for the determination of both the inorganic and total phosphates.

The precipitating reagent employed was that described by Embden<sup>1</sup>. Two stock solutions were prepared—A, a solution containing 50 gm of ammonium molybdate and 300 cc of concentrated nitric acid made up to 600 cc with water, and B a 15 per cent solution of strychnin nitrate. The actual precipitating reagent was prepared as required by mixing these solutions in the proportions of three parts of A to one part of B. For each precipitation 20 cc of the reagent were employed. The precipitating reagent was poured into the phosphate containing solution and the mixture was allowed to stand with frequent shaking for one hour, thus insuring complete precipitation. A yellowish, amorphous precipitate was obtained. At the end of one hour the contents of the flask were filtered through a Gooch crucible which had previously been dried at 110 C and weighed. It is important to use only gentle suction during filtration. The precipitate was washed, first with 25 cc of ice cold diluted (1:5) molybdic-nitric acid reagent, and subsequently with ice cold water until the washings were no longer acid. The Gooch crucible was dried at 110 C for one and a half hours, cooled in the desiccator and weighed.

The weight of the precipitate divided by 28.24 gives the weight of phosphate expressed as  $H_2PO_4$ . In most cases the weight of the final precipitate obtained was of the order of from 10 to 20 mg and could, therefore, be weighed accurately with ease. With the quantities of blood usually employed this corresponds in the case of the inorganic phosphate to 25 cc of blood (5 cc of blood made up to 50 cc—25 cc of filtrate taken) and in the case of the total phosphate to 0.5 cc (25 cc of blood made up to 25 cc—5 cc of mixture taken).

For the success of this method it is important to use reagents of the highest purity. The estimations of inorganic phosphates in the blood should be done as soon as it is withdrawn or if this is impossible the blood should be kept on ice. Bloor<sup>2</sup> states that unless such precautions are observed fallacious results are obtained. This statement has been confirmed by actual experiment. As stated above, the use of cane sugar during the estimation of total phosphates does not appear to exercise a marked influence on the results obtained, but attention must be drawn to the fact that the most satisfactory results in the

recovery of added phosphates from the blood were obtained when cane sugar was employed (Experiments 3 and 4, Table 2-B) Sufficient experiments have not been done to decide this point definitely

In order to verify the accuracy of the method, a number of experiments on the recovery of added phosphate from blood were carried out and are recorded in Table 2 It will be seen that the calculated and

TABLE 2—ESTIMATION OF ADDED PHOSPHATES

Number	Added Phosphate Expressed as Mg $H_3PO_4$ to 5 C c Blood (A) 25 C c Blood (B)	Phosphate in Blood, Mg $H_3PO_4$ per 100 C c	Blood Plus Added Phosphate, Mg $H_3PO_4$ per 100 C c	Calculated Blood Plus Added Phosphate, Mg $H_3PO_4$ per 100 C c
A Inorganic Phosphates				
I	7.3	11.92	159.6	158
II	6.55	4.53	137	136
III	7.9	14.8	172.2	172.8
B Total Phosphates				
I	8.9	124.6	472.3	480
II	5.9	138.8	366.1	374.8
III	3.2	112.6	240	240.6
IV	6.0	119.6	355.5	359.6

observed results agree to within 1 per cent in the case of the inorganic phosphate determinations, and to within about 2 per cent in the case of the total phosphates The greater error in the latter determination was probably due to the more difficult technic involved, as well as to the

TABLE 3—INORGANIC AND TOTAL PHOSPHATES OF NORMAL WHOLE BLOOD  
MG OF  $H_3PO_4$  PER 100 C C

Subject	Inorganic Phosphates	Total Phosphates	Subject	Inorganic Phosphates	Total Phosphates
1	10		6		128.8
	10	124		15	129.6
	9.6		7	14.4	124.6
2	10.5	102		11.4	
	11.9	110.5	8	15.8	
	15.2	121		21.2	134.5
3	15			18.8	138.8
4	13.3	135.9	11		116.8
5		119.6	12	14.8	133
		118.2			126.7
		122.5	13		135
		127.4	14		125
			15	13.2	123.9

smaller quantity of blood used Nevertheless, the accuracy of the method is more than sufficient to meet the requirements of clinical estimations

The phosphates of a group of normal adults were determined and the results will be found in Table 3 The samples of blood were drawn in the postabsorptive state to eliminate possible variations due to food In one or two cases, several determinations were done on the same

TABLE 4—CHRONIC NEPHRITIS, WHOLE BLOOD

Case	Date	Age	Inorganic Phosphate, Mg per 100 Ce (H <sub>2</sub> PO <sub>4</sub> )	Total Phosphates, Mg per 100 Ce (H <sub>2</sub> PO <sub>4</sub> )	Ratio Total to Inorganic	Non protein Nitrogen, Mg per 100 Ce	Chloride (NaCl), Mg per 100 Ce	Pressure CO <sub>2</sub> , Vm Hg	Ce Vol per Cent, CO <sub>2</sub> Taken Up	Ce Vol per Cent, CO <sub>2</sub> Normal (Haldane)	Alkaline Reserve, per Cent	Phosphates in Urine, Gm per Cent	Phosphates in Urine, Gm per Diem
1	10/17/21	72	12.6	118	9.3	50	547	11.9	58	57	+2	0.167	0.531
2	10/23/21	68	13	127.1	9.7	48	585	13	52.7	52.5	+0	0.115	1.93
3	10/25/21	49	14.1	117.5	8.3		575	47	52.2	54	-3	0.212	
4	10/27/21	55	14.8	114	7.7	10	562	12.7	54.3	52.5	+3	0.195	
5	10/31/21	13	13	121	9.2	10	531	46.1	57	51	+5		
	11/1/21		13.5	128	6.5			45.1	53.5	53.5	+0		
	11/4/21		13.7	108.3	8	37	578	45.1	54.12	51.9	+0	0.230	2.07
6	11/2/21	21	13.7	122.5	8.9		511	48.5	52.21	55.3	-5	0.062	1.154
7	12/5/21	34	15.8	106.9	6.8	20	601	50				0.131	1.28
8	12/6/21	20	16.8	121.8	7.2	41	509					0.076	0.867
9	12/30/21	19	18.5	106	5.7	15						0.105	2.68
10	1/4/22	38	26.4	172	6.5	60	493.7					0.243	1.94
11	1/4/22	39	11.8	118.9	10	46	546	44.3	52.5	53	+0	0.067	0.714
12	3/17/22	24	15.2	111.2	7.3	31	563	34.7	49.1	48	+2	0.249	2.14
13	3/29/22	51	22.9	166	7.2			20.8	42.86	45.2	-3		
14	4/3/22	53	14	136.6	9.7	31	530	36.9	46.3	49.3	-6	0.087	0.935

Normal volume per cent CO<sub>2</sub> in this table is that from the CO<sub>2</sub> dissociation curve of Haldane's blood, and the estimations were made with whole blood by a technique practically identical to that used by Christiansen, Douglis and Haldane (J. Physiol. 18: 244, 1914). The alkaline reserve is obtained by expressing the difference between volume per cent CO<sub>2</sub> found and the normal volume per cent CO<sub>2</sub> as a percentage of the normal. It has been found in this laboratory that this notation is the most convenient and accurate, but the Haldane curve may not express the true normal for all individuals. There is reason to suppose that the limits of normality may be as much as 5 per cent below the value found for Haldane's blood although we have seldom found values higher than those of Haldane in normal people.

subject and it will be observed in these cases that the results show but little variation, although considerable intervals of time elapsed between successive analyses

In Table 4 are recorded the studies of fourteen cases of chronic nephritis. The diagnoses were based on clinical symptoms and signs, as well as on laboratory examinations of the blood and urine. In this table the phosphate values are correlated with those of the nonprotein nitrogen, chlorides, carbon dioxide combining power of the blood and the phosphates of the urine.

In Table 5 will be found similar determinations on six cases of acidosis, associated with nephritis, and one case (Case 7) of tetany with lowered alkaline reserve.

From a study of Table 1 the most noteworthy fact seems to be the relative constancy in the ratio of total to inorganic phosphate. This ratio averages about 8.5 to 1. The cases of chronic nephritis recorded in Table 4 show but little change in this ratio. In fact, there is but little difference between the results found in these cases of chronic nephritis and those for healthy persons. As a whole, there may be a slight increase in the inorganic phosphate and a slight decrease in the total phosphate. Patient 10 was a borderline case between an acute and chronic nephritis, having been quite ill before coming to the infirmary and very much improved when his blood was examined. Unfortunately, his alkaline reserve was not estimated, but his urine showed an acidity of 40 c.c. per cent decinormal, and the ammonia nitrogen—urea nitrogen ratio was 0.13. The urinary acidity and the ammonia nitrogen and urea nitrogen were determined in the majority of these cases as a means to checking up the alkaline reserve. Patient 13 gave a history of having had clinical signs of acidosis before admission to the infirmary but the alkaline reserve proved to be nearly normal. Therefore, with but a small increase in the nitrogen retention, a normal or nearly normal alkaline reserve, a low output of acid in the urine and an ammonia nitrogen—urea nitrogen ratio approaching 0.03, the inorganic and total phosphates of blood do not vary considerably from the normal.

A study of the more severe cases of nephritis, those with uremia and acidosis, revealed an interesting change in the phosphorus compounds of blood. Invariably there was a marked increase in the inorganic phosphate, accompanied often by a slight decrease in the total phosphates, resulting in a low ratio of total to inorganic phosphates.

#### DISCUSSION

The general deduction from the results recorded above seems to be that the phosphates in the blood in nephritis only show a marked variation from the normal when the condition is associated with acidosis. In cases of acidosis, the inorganic phosphates are almost constantly

TABLE 5 — NEPHRITIS WITH ACIDOSIS, WHOLE BLOOD

Case	Date	Age	Inorganic Phosphate, Mg per 100 Cc (H <sub>2</sub> PO <sub>4</sub> )	Total Phosphates, Mg per 100 Cc (H <sub>2</sub> PO <sub>4</sub> )	Ratio Total to Inorganic	Non-protein Nitrogen, Mg per 100 Cc	Chlorids (NaCl), Mg per 100 Cc	Pressure CO <sub>2</sub> , Mm Hg	Cc Vol per Cent, CO <sub>2</sub> , Taken Up	Cc Vol per Cent, CO <sub>2</sub> , Normal (Haldane)	Alkaline Reserve, per Cent	Phosphates in Urine, Gm per Cent	Phosphates in Urine, Gm per Diem
1	10/30/21	65	34.9	108.3	3.1	124	609	50.6	32.1	55.5	-42	0.123	1.37
	10/31/21		33.7	113.3	3.2							0.091	0.355
	10/25/21		37.2	114.7	3	126	678	43	28.7	52.5	-45	0.061	0.683
2	11/ 7/21	58	20.4	121.1	5.9	96	378	38.3	43.5	50.1	-13	0.086	0.831
	11/ 9/21		20.3			92		40.1	42.7	51	-16	0.087	
	11/12/21		21.5	121.8	5.6			35.6	45.2	48.6	-7		
	11/17/21		25.2	114	4.5			43.1	53.2	52.5	± 0	0.126	1.15
3	11/14/21	40	42.2	149.6	3.5	160	562	42.1	37	52	-28	0.035	1.105
	11/16/21		44.1	173.5	3.9	191	578	29.9	28.4	45.3	-37		
4*	11/15/21	41	43.6	116.2	2.6	148	576	44.5	28.3	53.1	-47	0.056	0.494
	11/23/21		29.3	111.1	3.9	132						0.052	0.615
	11/28/21		17.9	101.2	5.6	94	553	38.05	67.3	49.9	+37	0.03	0.540
5	12/ 1/21	41	27.34			106		40.7	37.7	51.3	-26	0.038	0.769
	12/ 8/21		31.4	101.9	3.2	116	568						
	12/14/21		32.1	126.7	3.9	116	546	42.3	42	52.1	-19	0.029	1.009
6	2/15/22	38	25.7	133.2	4.7	210	594	42.2	44.8	52	-14	0.095	
	2/27/22		14.8	79.3	5.3	70	547	42.5	45.6	52.2	-12	0.055	1.947
7	3/ 8/22	40	23.9	97.7	3.7	67							
	3/10/22		24.6	92.7	3.7								
	3/23/22		28					42.8	35.3	52.3	-33		

\* This patient had been put on intensive treatment with sodium bicarbonate thus producing the alkalosis



increased above the normal value, sometimes to a considerable extent (Cases 1, 3 and 4, Table 5) This increase may be associated with an increase in the total phosphate (Case 3, Table 5) or the total phosphate may be normal or even low The high values of the inorganic phosphate suggest strongly that this substance is being mobilized to maintain the reaction of the blood within physiologic limits

The fact that some cases show high values for total phosphates, and other cases show low values may be accounted for in the following way It is possible to conceive of two types of acidosis which may be brought about by a disturbance in the normal function of phosphates in the body Either the kidney may lose the power of excreting phosphate, in which case acid phosphate would be retained in the blood thus producing a true "phosphate acidosis," as indicated by high total phosphates, or, owing to the abnormal rate of production of acids in the body or the failure of other mechanisms for their excretion (e g, the excretion of ammonium salts by the kidney), the phosphates of the body may be used up at such a rate for the purpose of excretion of acid that the total store of phosphates becomes depleted The first type is represented by Case 3, Table 5, and the second type by Cases 1, 2 and 7 In Case 2 the patient was treated with disodium phosphate (4 drams daily from the tenth) It will be seen that on this treatment the alkaline reserve returned to normal, and coincidentally the output of phosphate in the urine increased Presumably, therefore, in this case the excretion of acid had become deficient owing to depletion of the phosphates of the body and this condition was relieved by the oral administration of phosphate

In connection with this may be mentioned a case of acute nephritis in a child which was admitted to the Royal Infirmary before this investigation took place This patient on admission showed a severe nitrogen retention and acidosis, the output of phosphate in the urine being very much reduced The laboratory findings are recorded in Table 6 On the assumption that the acidosis was due to depletion of phosphate, disodium phosphate, in doses of 30 grains, every two hours, was administered On this treatment the condition of the patient rapidly improved, the acidosis disappeared and a laboratory examination two weeks later showed normal values for the nitrogen of the blood and an enormous increase in the output of phosphate in the urine

The administration of calcium has been suggested by Marriott and Howland<sup>4</sup> to relieve retention of phosphates According to the hypothesis outlined above, this treatment would be indicated only in cases such as Case 3, but so far it has not been possible to obtain data on this point

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4 Marriott, W McK, and Howland, J Phosphate Retention as a Factor in the Production of Acidosis in Nephritis, *Arch Int Med* 18 708 (Dec) 1916

TABLE 6

Observation No	Date	Urine						Blood				Remarks
		Ce per 24 Hours	Ammonia Nitrogen Mg per Cent	Urea Nitrogen Mg per Cent	Acidity, per Cent of N/10 Acid	NaCl Mg per Cent	P <sub>2</sub> O <sub>5</sub> Mg per Cent	Total Non-protein N Mg per Cent	Urea Nitrogen per Cent	NaCl, Mg per Cent	Alkaline Reserve Percentage Deficiency	
1	6/10/21	277	19	182	16	131	70	222	180	184	-22	Schoolgirl, age 12, admitted June 9, 1921, for acute recurrence of old nephritis, albuminuria, hematuria, vomiting, headache, no edema, slight but definite hyperpnea Commenced Na <sub>2</sub> HPO <sub>4</sub> , 30 grains every two hours No hyperpnea Urine volume per day doubled, specific gravity remaining the same, erythematous rash all over body Na <sub>2</sub> HPO <sub>4</sub> stopped Much improved Albuminuria and hematuria almost disappeared, patient discharged from hospital
2	6/11/21											
	6/13/21 6/16/21	590	7.7	395	15	137	90	278	208	177	± 0	
3	6/29/21	1,130	5.6	281	10.4	353	225	36	28	536	+ 9	
4 5	7/15/21 9/ 4/21	642	17.5	871	33	501	170	35 36	28 28	538 563	- 3	

## SUMMARY

1 A gravimetric method for the estimation of the inorganic and *total phosphates in whole blood* is described

2 The results are recorded of a number of analyses carried out on normal persons, cases of chronic nephritis and cases of nephritis with acidosis

3 A suggestion is put forward as to the line of treatment to be adopted in relation to the findings of blood phosphates

# THE INCREASE OF CERTAIN VAGAL EFFECTS WITH INCREASED AGE \*

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During the course of a consideration of the occurrence of respiratory arrhythmia in old age, it became evident that there was an increase in certain vagal effects, coincident with increased age

That there is such an increase in vagal activity, is not a new observation. Mention of such an increased activity has been made from time to time, but little definite evidence is to be gained from the literature

Allbutt<sup>1</sup> predicates such an overaction of the vagus with age. He cites Dr. Hugh Anderson's experiments showing an increased vagus action in old cats and not in young kittens. He also quotes Wenckebach's observation that he had found the vagus especially active in anginal cases. More recently Vinnes<sup>2</sup> has shown that the effect of pressure over the vagus trunk was more pronounced in adults than in children. Glaser,<sup>3</sup> however, by a different method, concludes that the vagus is more active in youth, and less active in old age.

In testing the response of the heart to stimulation of the vagus trunk as it descends in the neck beside the carotid, we had noticed certain differences in the degree of response which we thought to vary with age, and at that time, with cardiac pathology. In order to determine just what were the factors which influenced the degree of response, the reaction was measured and tabulated in a series of 177 cases, the patients ranging in age from 5 to 93.

Mechanical stimulation of the vagus by pressure over the nerve as it descends in the carotid sheath is a procedure which has been familiar since its description by Czernak about half a century ago, and requires no comment. Its disadvantages are certain very obvious inaccuracies. It is quite possible that in some cases the nerve may escape stimulation altogether. The moment of stimulation, the duration, or the intensity cannot be determined with accuracy. It cannot be deter-

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\* From the Medical Service of St. Luke's Hospital

1 Allbutt, C. Diseases of the Arteries and Angina Pectoris, London, 1915

2 Vinnes, E. M. G. Genesisk bladen **22** 41, 1920, rev. in *Physiol. Arch.* **6** 40, 1921

3 Glaser, F. *Med. Klin.*, **18** 371, 1922

mined whether the effect is through a peripheral action, whether it is central through the opposite nucleus, or whether it is peripheral in one instance, and central in another

In the cases here recorded the electrographic string was watched, and stimulation discontinued the moment any effect was noted. Minimal pressure was used at first, and in many cases, especially in the sixth decade, it was instantly productive. If no effect was observed, pressure was increased, or the position changed. The time of stimulation was recorded on the tracing, but was given no weight.

There were no uncomfortable sequels. Some patients were momentarily unconscious, but were not aware of it themselves, and felt no ill

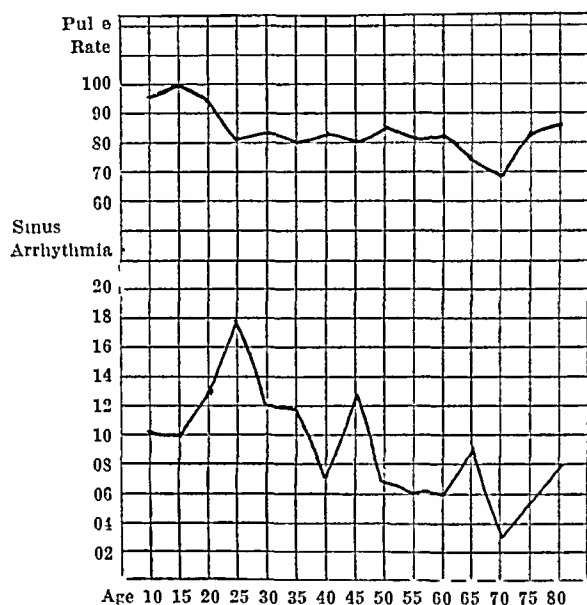


Fig 1—Pulse rate and the degree of sinus arrhythmia averaged in five year periods and plotted according to age

after effects. So far as I have been able to discover, no serious results are recorded in the literature. Robinson<sup>4</sup> comments on the safety of the procedure. Wenckebach,<sup>5</sup> with a large experience, observed no ill effects but used great care. My own faith in the certainty of the heart to escape from vagal stimulation was considerably shaken by one case early in the series. A man, aged 65, after very light and momentary pressure, had a complete standstill, with no ventricular escape for 5.76 seconds, when the normal sequence returned. Wenckebach records

4 Robinson, G. C., and Draper, G. J. *Exper. M.* **14** 217, 1911, **15** 14, 1912

5 Wenckebach, K. F. *Die Unregelmässige Hertzthätigkeit*, Leipzig u. Berlin, 1914

a standstill of 6 seconds, as does Vinnes. I do not feel that the procedure is without the possibility of danger. In our cases in the fifth decade and past we erred on the side of safety, and used lighter pressure.

To secure those with normal hearts, chosen cases from the surgical and orthopedic wards, hospital attendants, physicians and students were used. A normal tracing was taken with all three leads, followed by a strip of Lead II taken during forced deep respiration. A tracing of Lead II was then taken during stimulation of the right and left vagus, or the tracings were taken in the reverse order.

Measurements were made to 0.01 seconds, which allowed of more than sufficient accuracy where the deviations were so extreme.

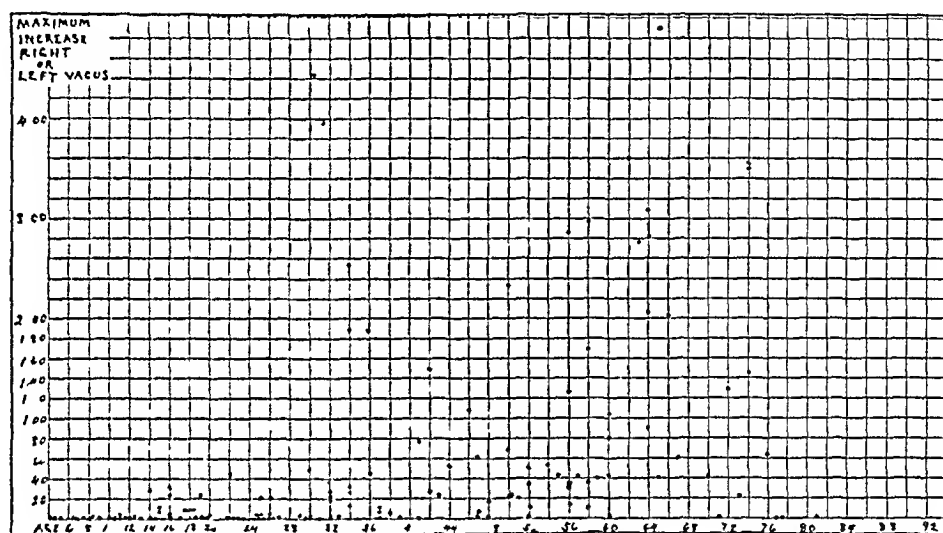


Fig 2—Maximum increase in the R-R interval obtained by digital stimulation of either vagus, plotted in hundredths of a second, according to age.

*Pulse Rate*—The relation of pulse rate to age in this series is shown in Figure 1. The rates are averaged in five year periods. In so small a series the resulting curve is, of course, very uneven. It shows, however, a definite decrease in rate to the age, 65-70, followed by a rise. This agrees with the table compiled by Guy<sup>6</sup> and summarized by Howell.<sup>7</sup>

*Sinus Arrhythmia*—The degree of respiratory arrhythmia was measured by the difference in length between the longest and the shortest R-R intervals in the normal tracing. Because of the small number of cases, we again have a very irregular curve, but the ten-

6 Guy. In Todd's Cyclopaedia of Anatomy and Physiology, London 1847.

7 Howell, W. H. Textbook of Physiology, W. B. Saunders Company, Philadelphia, 1915.

dency to decrease with age is unmistakable. The increase in the degree of respiratory arrhythmia in forced deep respiration followed a similar curve.

#### EFFECT OF DIGITAL STIMULATION OF RIGHT AND LEFT VAGUS

The degree of effect of vagus stimulation was measured by the difference in length between the longest *R-R* interval in the normal tracing, and the longest *R-R* interval obtained on vagus stimulation. The *P-P* interval frequently was longer than the *R-R* interval, but was not used because of the difficulty of determining in many cases whether the intervening ventricular complexes were in response to impulses generated low down with an iso-electric *P* wave, or whether they were actual ventricular escapes.

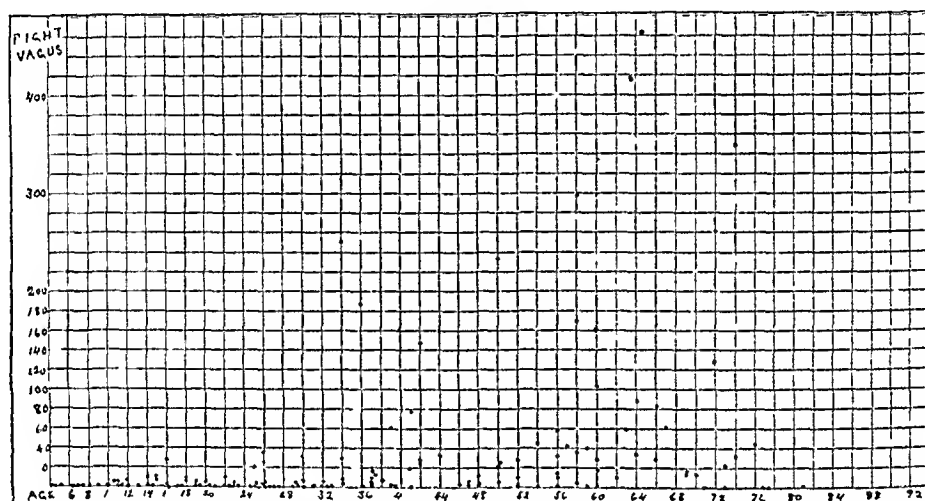


Fig 3—Maximum increase in the *R-R* interval obtained by digital stimulation of the right vagus, plotted in hundredths of a second, according to age.

A discussion of the variation in vagus effects on stimulation would require a more detailed analysis than can be given here. There was no marked difference between the right and left vagus. The predominating effect was a slowing of stimulus production, frequently with a decrease in amplitude of the *P* wave, which in some of the cases became iso-electric or inverted. As the pace-maker was displaced downward, a decrease in the *P-R* interval was noted in part of the cases. In some of the younger subjects there was a generalized slowing of rate, although the *R-R* intervals were no longer than the longest observed before the stimulation.

An increase in the *P-R* interval of 0.01 second or more was present in less than one third of the cases. Complete disassociation occurred in one case with both right and left vagus stimulation in a case of 2 to

1 block, and in two cases with right vagus stimulation, and in two cases with left vagus stimulation. All of the subjects showing complete block had definite cardiac pathology, and all were over 60, except one, aged 34.

The difference in 0.01 seconds between the longest normal *R-R* interval and that obtained on vagus stimulation was plotted according to the age of the subject.

In Figure 2 is plotted the maximum increase with either vagus, and in Figures 3 and 4 the increase with the right and left vagus is shown, respectively. The three figures are quite similar, and show an increase in response with increased age, with the possibility of a decrease in the latter part of the seventh decade and after.

That the increase in response is a function of the age of the subject,

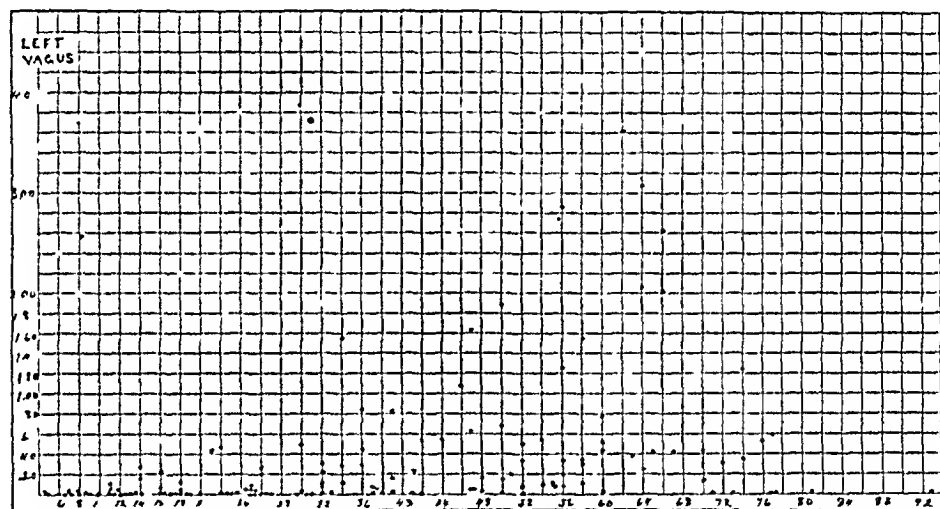


Fig 4—Maximum increase in the *R-R* interval obtained by digital stimulation of the left vagus, plotted in hundredths of a second, according to age.

and not of the cardiac pathology, is indicated in Figures 5 and 6. In these charts are plotted separately the results obtained in cases presenting definite pathology and those with no demonstrable pathology. The maximum response with either right or left vagus is plotted.

It is difficult to say that any person past middle life has a normal heart, or what is normal for the age. We can only say in the cases used in this series that they had no circulatory symptoms or demonstrable findings. Arteriosclerosis was present in varying degree in both series. Functional kidney tests (phenolsulphonephthalein) and blood chemistry were within normal limits in the cases charted as normal. The two charts are again essentially alike, and show only an increase in response with increased age.

In Figures 7 and 8 are plotted the changes in conduction time with right and left vagus. Decreases in the *P-R* interval are plotted below



the base line, and increases in the *P-R* interval are shown above the baseline in 0.01 seconds, according to age. Here, again, an increase in response is seen with increased age, as indicated by an increase in the *P-R* interval. Cardiac pathology could not be demonstrated to be a factor in the decrease of conductivity, although it is to be noted that all of the cases, except one of those showing complete block, were cases manifesting definite cardiac lesions. It is possible that in a larger series a more definite difference could be noted in the effect on conductivity.

The heart cases were such as are usually found in the wards of a large city hospital, and represented all degrees of circulatory insuff-

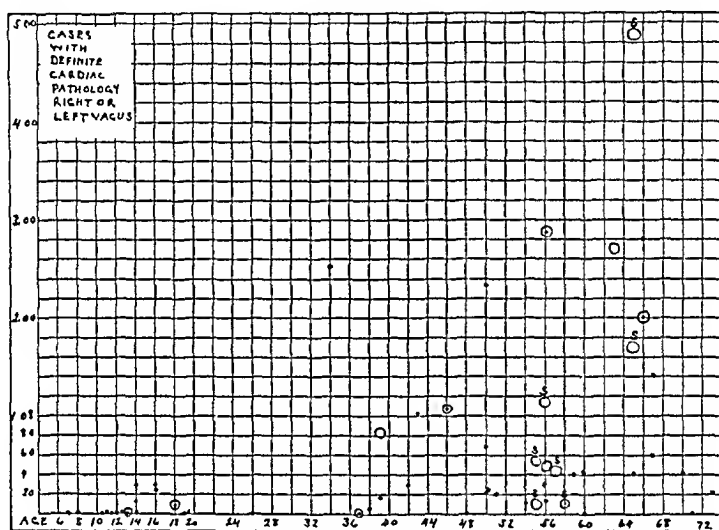


Fig 5—Maximum increase in the *R-R* interval obtained by digital stimulation of either vagus in patients who showed a definite pathologic cardiac condition, plotted in hundredths of a second, according to age.

iciency. No relation could be demonstrated between the anatomic lesion, the severity of the lesion, or the degree of circulatory disturbance and the vagus effect.

It is difficult to evaluate arteriosclerosis accurately. The degree of arteriosclerosis was apparently not a factor. High or low blood pressure was not a factor.

In general, but not invariably, the patients who were well under the influence of digitalis showed an increased effect. One subject, a boy, aged 12, suffering from mitral stenosis with auricular fibrillation, who entered the hospital with extreme evidences of circulatory insufficiency, showed no response on entrance, but a moderate response when under the influence of digitalis.

The cases showing other evidences of overactivity of the vagus frequently, but not invariably, showed an increased effect.

A consideration of individual cases renders it even more difficult to see that cardiac pathology has any bearing on the degree of vagus effect. A subject with a mitral lesion, aged 37, who was moribund, showed no effect. A similar subject, aged 46, showed a marked effect. A patient with carcinoma of the stomach, aged 54, with generalized metastases, showed a well marked effect two hours before death. One patient aged 66, showed a marked effect when apparently well, and no effect later, when moribund with a nephritis. The angina pectoris patients showed an effect proportionate to the expectancy for the age, and no more. Some patients with marked angina showed no effect.

There would seem to be no relation between the degree of vagus effect and prognosis. In the eighteen months of observation there have been no deaths in the group with increased response and no

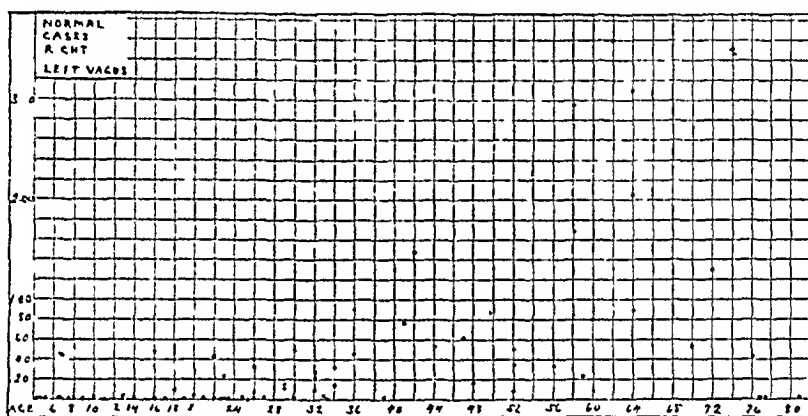


Fig 6—Maximum increase in the *R-R* interval obtained by digital stimulation of either vagus in patients who showed no demonstrable pathologic cardiac condition, plotted in hundredths of a second, according to age

cardiac pathology. Of the group suffering from cardiac disease, fifteen have died. These are indicated by a circle in Figure 5. They are about equally distributed between those cases showing slight or no effect, moderate effect and marked effect. In the case of patients dying suddenly and unexpectedly, the circle is surmounted by an *S*. Here, again, the vagus effect is not a factor, but an analysis would demand an accurate knowledge of the mechanism of the death in each case.

The foregoing does not agree with the conclusions of Wenckebach, who considers that an increased reaction is indicative, but not invariably so, of pathologic changes in the cardiac muscle, and who is inclined to give a bad prognosis when a marked effect results from light pressure. It is interesting to note that the cases figured by Wenckebach fall within the ages when a marked response would be expected in either normal or abnormal hearts, according to the results shown here.

Hough<sup>8</sup> with experimental cats and dogs under anesthesia showed an increased effect when the heart was weakened by long experiment. The anesthetic, however, introduces an unknown variable, as shown by Becht<sup>9</sup>.

The question as to whether the increased effect of vagus stimulation with increased age is due to increased central activity or to peripheral changes involving the nerve endings or to changes in the tissues effected is of interest. It is also conceivable that it could be due to a decrease in the activity of the sympathetic system. If there be a decrease of sympathetic activity with age, we know nothing of it at present.

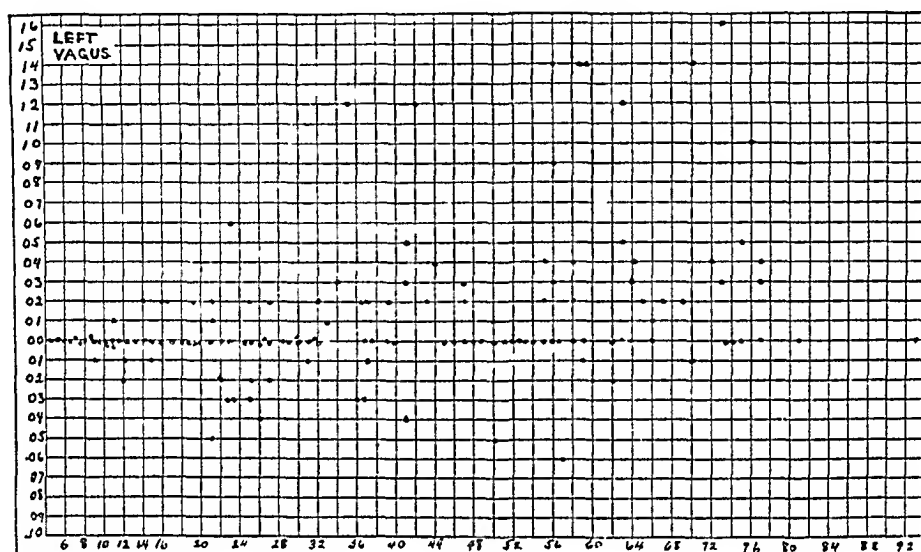


Fig 7—Changes in the *P-R* interval obtained by digital stimulation of the left vagus, plotted in hundredths of a second according to age. Increases in the *P-R* interval are plotted above the base line, and decreases in the *P-R* interval are plotted below the base line.

In the consideration of an increase in central activity of the vagus, an argument based on overactivity in other organs would again require proof that such an overaction was based on central and not peripheral changes. The pulse is slower with age up to a certain point, but such a slowing is not necessarily a central phenomenon. If there were an increased central activity of the vagus we might expect to obtain vagus effects with smaller doses of digitalis in later life. This was not the observation of Eggleston,<sup>10</sup> who found a very slightly increased dosage necessary after 40. My personal observation is that the dosage is the same. The validity of this argument, however, depends on the physics of digitalis action.

8 Hough, T. J. *Physiol* **18** 161, 1895.

9 Becht, F. C. To be published.

10 Eggleston, C. *Digitalis Dosage*, *Arch Int Med* **16** 1 (July) 1915.

Wenckebach concludes that the cause of the increased reaction lies in changes in the reacting tissue, consequent on pathologic changes in the tissue. If disease is a factor at all, it is not a simple factor. Age quite apparently is a factor, and it is quite possible that there may be changes coincident with age in either the nerve endings or in the reacting tissues, which results in a so-called lowering of the neuromuscular threshold. It is interesting in this connection to recall the variation in atropin effect with age. The effect of atropin is on the vagus nerve endings. After paralysis of the vagus nerve endings with atropin there is an increase in the degree of acceleration of the pulse up to the age of 30, and then a decrease, until in old age there

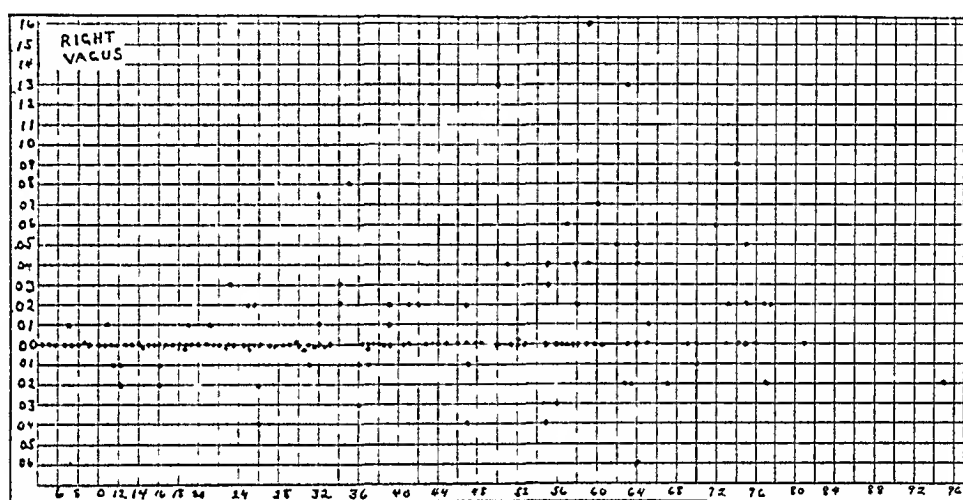


Fig 8—Changes in the *P-R* interval obtained by digital stimulation of the right vagus, plotted in hundredths of a second according to age. Increases in the *P-R* interval are plotted above the base line, and decreases in the *P-R* interval are plotted below the base line.

is little or no acceleration (Cushney<sup>11</sup>). In my own experience there is little or no acceleration after the fifth decade, and exceptions are rare, although they do occur. This would, of course, argue equally well for a decrease in sympathetic activity, if we had any other evidence of such a decrease.

Respiratory arrhythmia, and the increase in this arrhythmia with increased ventilation of the lungs, shows a decrease with age. This might be construed as indicating a decrease in the central activity of the vagus. But it is to be remembered that while such arrhythmia depends on the activity of the vagus nucleus for its appearance, it is not purely a vagus phenomenon, and that other factors not checked here enter into its appearance.

<sup>11</sup> Cushny, A. R. *Textbook of Pharmacology and Therapeutics*, Philadelphia, Lea and Febiger, 1918.

The preponderance of the little evidence we have appears to be in favor of the increased activity being due to changes in the nerve endings or the reacting tissues. Proof will depend on animal experiment.

The fact of such an increased vagus effect accompanying increased age opens a wide field of possibilities, on which we will not attempt to speculate. Such variations with age and with other pathologic or normal changes in tissues are of immediate physiologic and clinical importance.

A point of especial interest in the present instance is the bearing on the increased liability to the "vagal death" of Allbutt, and Capps and Lewis,<sup>12</sup> and on the hypotheses of Verdon.<sup>13</sup>

One would like to regard the increased vagus effect as conservative in character. It is possible that it might be regarded as one factor in a more labile depressor mechanism. Should we accept the theories of Hering and of Gaskell there would be a tendency toward an increase of the anabolic processes with age. In the light of our present knowledge, however, any comment on the significance of this phenomenon is treading on unsafe ground.

#### SUMMARY

1 In a series of 177 cases, the subjects ranging in age from 5 to 93 years, there is shown to be an increase in the response of the vagus to digital stimulation coincident with increased age.

2 This increase is a function of age alone and not of pathologic changes in the heart.

3 Whether the increase is due to central changes or to peripheral changes in the vagus or tissues affected cannot be proved from the evidence at hand.

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12 Capps, J. A., and Lewis, D. *Am J M Sc* **134** 130, 1907.

13 Verdon, W. *Angina Pectoris*, London, 1920.

# STUDIES OF EXOPHTHALMIC GOITER AND THE INVOLUNTARY NERVOUS SYSTEM

LEO KESSEL, M D, CHARLES C LIEB, M D

AND

HAROLD T HYMAN, M D

## III A STUDY OF FIFTY CONSECUTIVE CASES OF EXOPHTHALMIC GOITER

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AND

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NFW YORK

### INTRODUCTION

This report is a detailed account of the course of fifty cases of fully developed exophthalmic goiter. In order to eliminate the personal factor in diagnosis, no patient was included in this group in whom the clinical diagnosis was not confirmed by a distinct and continuous elevation of the basal metabolism. The course of the illness was followed with as little interference with the natural tendency of the disease as was compatible with the comfort of the patient. While of course, this could not be accomplished in as clearly defined a manner as the maintenance of a laboratory control, at least it is true that in these patients no specific therapy was instituted. The course of the symptoms and of the basal metabolism was closely followed, and the results obtained were estimated on the basis of restoration to social and economic usefulness, and on the return of the metabolism to within normal limits.

The observations made on this group of patients is the first step in the crystallization of a definite therapeutic policy for exophthalmic goiter, for with the establishment of the spontaneous course it will be possible in future studies to evaluate accurately the efficacy of "specific" therapeutic procedures.

In the two papers<sup>1</sup> that precede this one will be found a description of two groups of patients often erroneously included in reports dealing with exophthalmic goiter. The first group included patients who have a lump in the neck, and who have none of the primary or secondary manifestations of exophthalmic goiter, and no elevation of the basal metabolism. In the second group were patients who, with or without thyroid enlargement, presented symptoms and signs best

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\* Dr Lande is solely responsible for the metabolic studies in this as in the preceding papers.

<sup>1</sup> Kessel and Hyman. Am J M Sc. To be published.

TABLE 1—A SYMPTOMATIC, METABOLIC AND ECONOMIC STUDY OF THE RESULTS OBTAINED IN FIFTY CONSECUTIVE CASES OF GRAVES' SYNDROME OBSERVED WITHOUT THE INSTITUTION OF "SPECIFIC" THERAPY ("SPONTANEOUS COURSE")

Case Number	Social or Economic Status	Period of Observation					Basal Metabolism				Number of Subjective Symptoms		Severity of Subjective Symptoms		Decrease of Neck Circumference, Cm	Increase in Weight, Lbs	Remarks																
		Total, Months	Weeks in Hospital	Weeks in Country	Months at Home Full Rest	Months at Home, Part Rest	Period to Secure Complete Social or Economic Restoration, Months	First	Lowest	Percentage of Decrease	Period to Obtain Decrease, Mos	(a) On Admission	(b) At Last Visit	(a) On Admission				(b) At Last Visit															
1	Clerk	19	3	0	0	0	1	37	14	62	13	5	0	9	0	2	Lost from observation for 1 year during which time he worked. Now reports																
2	Peddler	8	2	0	0	0	1	45	16	65	3	11	4	24	1	6	Works from 5 a m to 9 p m with only a few hours rest in between																
3	Peddler	13	8	0	0	0	2	26	15	30	2	10	1	32	1	3	Has moved to Detroit. Have not heard from him in 4 months																
4	Jeweller	18	8	3	0	0	4	47	29	57	2	1	0	4	0	6	Has developed migrainous headaches																
5	Foreman	16	4	0	0	0	2	39	31	20	5	6	0	15	0	3	Had severe pneumonia. Have not seen him in 5 months																
6	Clerk	20	16	0	0	0	1	54	16	70	3	12	1	26	3	0	Had true febrile recurrence following tonsillitis. Now receiving Roentgen ray at P H																
7	Baker	12	12	0	1	0	4	35	16	55	3	6	0	14	0	22	Working 10 hours a day. Febrile crisis																
8	Cobbler	13	1	3	1	0	2	38	4	52	2	8	1	25	1	4	11	Died of exophthalmic goiter. Febrile crisis. Died of hemorrhage from cancer of stomach. Has been working for several months.															
9	Operator																		11	6	4	1	0	5	8	2	8	5	3	8	4	11	Has had three sinus operations each accompanied by slight exacerbation.
10	Operator																																
11	School Clerk	20	3	0	1	3	14	25	12	28	3	2	2	8	8	4	11	Complete recovery															
12	Typist	10	9	0	1	0	10	40	28	30	2	10	3	36	5	5	25	Has had three sinus operations each accompanied by slight exacerbation.															
13	Operator	3	6	0	0	0	Died	44	40	9	1	10	2	19	3	5	25	Prolonged course. Now looking for employment															
14	Typist	19	6	4	0	0	4	53	6	88	3	9	0	24	0	0	16	Died of status lymphaticus after losing most of manifestations of exophthalmic goiter.															
15	Painter	10	5	5	0	0	3	18	5	100	3	12	1	21	1	6	Working for 15 months																
16	Typist	7	6	1	3/4	0	3	58	14	21	4	14	4	39	5	6	21	Symptoms greatly improved although basal metabolism elevation persists															
17	Housewife	7	9	2	0	0	7	57	15	73	4	14	1	15	1	4	24	Working from observation															
18	Clerk	2	9	0	0	0	15	24	19	21	1	7	2	18	5	2	20	At work															
19	Nurse	22	4	3	0	0	3	35	3	80	7	5	1	10	1	5	20	At work for over a year															
20	Operator	22	8	4	0	0	3	55	0	100	8	8	0	16	0	5	23	At work															
21	Operator	10	6	4	0	0	3	46	15	67	3	13	5	33	5	6																	

23	Housewife	7	1	0	0	1	2	20	15	25	4	13	2	25	2	25	6	6	10	Has had trying home conditions
24	Housewife	18	3	3	0	0	2	17	5	71	3	12	0	16	0	1	1	10	10	Had a mastoiditis
25	Housewife	13	10	1	0	1/2	13	34	17	50	2	10	3	30	6	3	11	11	11	Basal metabolism rose to 11 with sinusitis
26	Teacher	13	1	12	6	1	11	29	8	72	3	9	0	22	0	6	10	10	10	Great relief to exophthalmic goiter with sinus treatment
27	Housewife	12	7	0	0	3	5	18	26	15	2	7	3	14	3	6	15	15	15	To be married
28	Housewife	14	3	4	0	2	?	64	22	66	7	14	4	35	4	6	10	10	10	Has mitral stenosis and most symptoms are auricular
29	Housewife	13	6	0	2	2	12	100	9	91	9	4	1	7	1	3	20	20	20	An unmanageable person
30	Housewife	18	6	6	0	0	3	64	15	77	12	13	1	21	1	4	16	16	16	At present is well
31	Teacher	18	7	7	0	1	5	58	12	80	8	16	2	36	4	2	36	36	36	Marked goiterophobias
32	Housewife	10	1	1	0	0	2	30	20	60	3	15	1	27	1	1	21	21	21	Has remained well through a pregnancy and
33	Dancer	13	4	0	0	12	3	40	14	65	1	8	0	14	0					terrible financial straits
34	Housewife	14	4	20	0	1	6	36	4	89	2	5	1	13	1		5	5	5	Laryngeal symptoms most marked
35	Homeworker	17	1	8	0	0	3	22	16	27	1	5	1	14	1	9	17	17	17	Improved somewhat by vocalist
36	Housewife	21	6	0	1/2	2	6	48	17	65	1	14	0	40	0	5	38	38	38	Ophthalmometer reading decreased 5 mm
37	Housewife	17	5	2	0	1	2	35	12	66	1	9	1	25	1					Though symptom free and with normal basal metabolism, had thyroidectomy for cosmetic reason
38	?																			Severe mental and economic strain, but keeps fairly fit
39	Housewife	16	0	0	0	0	0	37	6	84	9	7	5	24	11					Has healed tuberculosis
40	Housewife	19	42	12	0	0	4	30	17	43	1	8	1	24	1					Marked weight gain
41	Housewife	17	4	0	0	0	2	48	6	89	5	7	2	15	2	4	4	4	4	Has gone through normal pregnancy and sinus infection with only slight exacerbation
42	Housewife	8	9	4	0	0	3	68	41	40	4	17	6	50	10	3	10	10	10	Febrile psychosis
43	Housewife	9	6	0	0	1	3	17	0	100	8	12	9	35	11	6	15	15	15	Sent to Bellevue where she died
44	Pianist	19	2	0	2	1/2	3	63	0	100	7	7	0	18	0		14	14	14	Has had twins
45	Housewife	12	2	1	0	0	2	28	6	79	3	8	2	18	4		25	25	25	Economic struggle keen
46	Housewife	10	17	0	2	0	0	50	31	38	6	13	2	27	2	3	15	15	15	Has gone through normal pregnancy
47	Peedler	12	5	1	0	0	2	47	14	66	9	7	2	18	4					Still complains of gastrointestinal symptoms
48	Janitress	7	9	8	5	0		48	43	10	2	8	1	26	4					Persistent elevation of basal metabolism despite improvement clinically
49	Janitress	2	9				Died	50	24	52	2									Symptoms greatly increased by sinus infection and abate with drainage
50	Housewife	2	10					48	48											Extraordinary recovery
51	Housewife	7	21	9				57	62											Great mental and economic stress
																				Had tran-
																				sient fibrillation
																				Had hydrops of gall bladder
																				Economically unfit
																				An epileptic
																				Has decompensated myocardium and auricular fibrillation
																				Died of pneumonia and pericarditis following pyelitis
																				Failure
																				Lost from observation
																				Persistent fibrillation, diarrhea and elevated basal metabolism but clinically better



grouped under the single term of "sympathomimetic," the term of Barger and Dale<sup>2</sup> to denote "manifestations that are tantamount to electrical stimulation of the thoracolumbar division of the involuntary nervous system, or to stimulation of this same system by adrenalin" Such symptoms include the cardinal clinical symptoms of tachycardia, exophthalmos, goiter and tremor, and the minor symptoms of exophthalmic goiter, such as diarrhea, sweating and palpitation In these patients there was no alteration in basal metabolism, and no evidence that an alteration had even been present To this clinical syndrome of sympathomimetic symptoms without elevation of the basal metabolism we have applied the term autonomic imbalance It is solely by the absence of an elevation of basal metabolism that these patients are distinguishable objectively from patients with exophthalmic goiter

#### MATERIAL STUDIED

The patients were studied in the wards of the Mount Sinai Hospital<sup>3</sup> The following points are to be emphasized (1) The symptoms presented were sufficiently severe to warrant residence in a hospital where beds are at a great premium, (2) the patients in our institution present a racial nervous and emotional instability, (3) the patients come from the poorest sections of the city, and are subject to constant economic strain, (4) the history of fifty consecutive patients is presented irrespective of the end results An attempt was made to follow each patient Where contact was lost we regard the case as a failure and so report it

The abstract of a case history given below is typical of the studies made of each of the patients Where symptoms could not be measured, the intensity was indicated on the basis of four plus (4 +) Special attention was paid to the sequential history, which detailed the complete life of the patient This served two purposes First, to throw light on the natural history of the illness, and, second, to guide in the management of the individual patient

*M N* (208121), female, aged 26, single, was an art illustrator

*Past Illnesses*—Patient had measles and scarlet fever four times in childhood, pertussis twelve years ago, epidemic influenzal pneumonia two years ago Her tonsils and adenoids were removed sixteen years ago

*Personal History*—Menses began at the age of 16, occurring every twenty-eight days and were of three days' duration

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2 Barger and Dale *J Physiol* 41 19, 1910

3 The clinical studies were carried out in the wards of the Mount Sinai Hospital on the medical services of Drs Brill and Libman and in the out-patient department in the classes of Drs E Moschowitz and R Ottenberg, the laboratory studies, in the department of pharmacology of the College of Physicians and Surgeons, Columbia University The work has been made possible by a fund established for the purpose by the New York Foundation and by Mr Felix Warburg

*Sequential History*—The patient was born in Canada. Her life was uneventful until eight years ago when she was told by telephone that her father had been killed. She was greatly shocked and was unable to talk for several days. A few months after this, the goiter was noted but she had no other symptoms. Iodids were administered without effect on the gland. Despite financial reverses, she was well for the next two years. Then she experienced nervousness, exophthalmos, asthenia, tremor and tachycardia, and she lost 30 pounds weight. Her physician regarded her condition as so precarious that he gave her three months to live. She was treated with injections but without benefit. She then came to New York and rested at the home of an aunt where she was carefully nursed. She gained 30 pounds weight and resumed her work in the art school. Because of the unsightliness of her goiter, she sought operative treatment, although she was then symptom free. She entered the hospital, and examination revealed, besides the goiter, only tremor and a pulse rate of 100. A hemithyroidectomy was performed and the specimen was reported to be a parenchymatous and colloid struma. After operation she felt that her condition was unchanged, her goiter was no smaller. A few months later she was desperately ill with pneumonia. She resumed her work in a few months and was well until six months ago when her previous symptoms recurred. She also had a growth on her knee which she was told was tuberculous. She entered the hospital for the removal of this tumor but was prevailed on to

Present Status	7/15/21	7/2	6/16	7/11	8/12	10/8	2/10/22	3/14	10/1
Loss of weight	30 lbs	Gain	G	G	G	G	—	—	—
Nervousness	4	0	2	1	0	0	0	0	0
Palpitation	2	1	1	1	0	0	1	0	0
Bulging eyes	2	2	2	2	2	1	0	0	0
Goiter	3	2	2	2	2	2	1	0	0
Tremor	3	0	1	0	0	0	0	0	0
Sweating	2	0	0	0	0	0	0	0	0
Flashes	2	0	0	0	0	0	0	0	0
Asthenia	2	0	0	0	0	0	0	0	0
Weight	112	119	—	124	—	128	—	—	—
Pulse	112	100	110	100	—	88	—	88	88
Exophthalmometer	20	—	20	—	21	—	—	17.5	—
Basal metabolism	53	36	16	16	22	5	6	—	—

submit to thyroidectomy. Before this operation examination revealed a pulse rate of 98, exophthalmometer, 20, basal metabolism +10 and +16, and a tremor. The operation was done under local anesthesia, the middle and left lobes were removed, and the report was parenchymatous goiter. She was returned from the operating room in a precarious condition and was desperately ill for five days. She finally went to the country and convalesced nicely. One month ago all her previous symptoms returned with the severity of her first crisis.

*Anatomic Status*—The patient was well nourished, her hair was black, streaked with gray, the outer portion of the eyebrows was sparse, systolic murmurs were present at both apex and base with respiratory arrhythmia and dynamic abdominal aorta, a spastic sigmoid was palpable. The digits tapered. Emotionalism and vasomotor instability were marked. Scars were present over the thyroid. A large thyroid remnant persisted, irregular in shape, soft to the touch and with a bruit over it. The nasal septum was deviated. The tonsils were cryptic and half buried. All eye signs were present. Locomotion pulse was present in the vessels of the fundus.

*Laboratory Data*—Tests revealed Hemoglobin, 93 per cent, red blood cells, 4,200,000, white blood cells, 7,100, lymphocytes, 31 per cent, platelets, 20,000, bleeding time, 5 minutes (secondary purpura). Urea, 15, meoagulable nitrogen, 40, uric acid, 3, creatinin, 1.55 mg per hundred cubic centimeters, sugar tolerance test, 113/220/180, occasional albuminuria was noted. Phenolsulphonephthalein, 62 per cent, reaction to epinephrin was + + + + and to atropin + + + +.

TABLE 2—PREEXISTENT SYMPATHETICOMIMETIC SYMPTOMS (AUTONOMIC IMBALANCE) IN PATIENTS NOW SUFFERING FROM EXOPHTHALMIC GOITER

	Palpitation	Nervousness	Sweating	Blushing	Cold Extremities	Headache	Psychic Unrest	Loss of Hair	Irregular Menses	Stomach Trouble	"Heart Trouble"	Diarrhea	Dyspnea	Polyuria	Polydipsia	Asthenia	Insomnia	Sympatheticomimetic "Score"	Epinephrin Reaction	Atropin Reaction
Males																				
1 Albeck	0	+	+	+	0	+	+	0	—	0	+	0	0	0	+	0	0	7	4	—
2 Preisler	+	+	+	+	0	+	+	0	—	0	+	0	+	0	0	0	0	7	4	3
3 Weinstock	+	+	+	0	+	+	+	+	—	0	0	0	0	+	+	0	0	9	4	0
4 Rosenthal	0	0	0	0	0	0	0	0	—	0	0	0	0	0	0	0	0	0	4	4
5 Cohen	0	0	0	0	0	0	0	0	—	0	0	0	0	0	0	0	0	0	4	3
6 Faber	0	0	0	0	0	0	+	0	—	0	0	0	0	0	0	0	0	1	4	4
7 Wollman	0	0	+	0	0	0	0	0	—	0	0	0	0	0	0	0	0	1	2	3
8 Kantrowitz	0	0	0	0	0	0	0	0	—	0	0	0	0	0	0	0	0	0	—	—
9 Rosenberg	0	0	0	0	0	0	0	0	—	0	0	0	0	0	0	0	0	0	—	—
10 Horowitz	0	+	0	0	0	0	0	0	—	+	0	0	0	0	0	0	0	0	—	—
Females Whose Symptoms Arose Before the 35th Year																				
11 Dunkelmann	0	0	+	+	0	0	+	+	+	+	0	+	0	+	+	0	0	9	1	3
12 Berkowitz	0	0	+	0	0	+	+	0	+	0	0	0	0	0	0	+	0	2	4	2
13 Droga	0	0	+	0	0	+	+	0	+	0	0	0	0	0	+	0	0	3	0	—
14 Kurzmaek	0	0	+	+	0	+	+	+	+	0	0	0	0	0	0	0	0	6	—	—
15 Naimon	0	0	0	0	0	+	+	0	+	0	0	0	0	0	0	0	0	2	4	4
16 Belford	0	+	+	+	+	+	+	+	+	0	0	0	+	0	0	0	+	10	—	3
17 Juhasz	0	+	+	+	0	+	+	+	+	0	0	0	+	0	0	0	0	7	4	2
18 Meltzer	+	+	+	0	+	+	+	+	+	0	0	0	+	0	0	+	+	10	—	—
19 Tanguay	0	0	0	+	0	0	0	0	0	0	0	0	0	0	0	0	0	1	4	1
20 Goodglass	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	—	—
21 Kraft	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	2
22 Albert	0	0	0	+	+	+	+	+	+	0	0	0	0	0	+	+	+	7	—	3
23 Fox	0	0	0	+	+	+	+	+	0	0	0	0	0	0	+	+	+	8	3	3
24 Cohen	0	0	+	+	0	+	+	0	0	0	0	+	0	0	0	0	0	4	2	4
25 Rodamon	0	0	0	0	0	0	0	0	+	0	0	0	0	0	0	0	0	1	4	4
26 Altman	0	0	0	0	0	0	0	0	+	0	0	0	0	0	0	0	0	1	—	—
27 Fisher	0	0	+	0	0	+	+	0	0	0	0	0	0	0	0	0	0	2	4	2
28 Steinbaeh	+	0	+	+	+	+	+	+	+	0	0	+	0	0	0	+	0	10	—	—
29 Farber	0	0	0	0	0	+	+	0	0	0	0	0	0	0	0	0	0	1	—	—
30 Goldstein	0	0	+	+	+	+	+	0	0	0	0	0	0	0	0	0	0	4	4	0
31 Handel	0	0	0	+	0	+	+	+	+	0	0	0	0	0	+	0	0	6	4	4
32 Green	0	0	+	0	0	+	+	+	+	0	0	0	0	0	0	0	0	3	4	4
33 Hoffman	0	0	0	0	0	+	0	+	0	+	0	0	0	0	0	0	0	3	4	1
34 Kretzman	0	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	—	0
35 Hamburger	0	0	+	+	+	0	0	0	0	0	0	0	0	0	+	0	0	4	—	0
36 Griffith	0	+	0	+	0	0	+	0	0	0	0	0	0	0	0	0	0	3	4	—
37 Honig	+	0	0	0	0	0	0	0	+	0	0	+	0	0	0	+	+	5	4	4
38 Spiegel	0	+	0	+	+	0	+	0	0	0	0	0	0	0	0	0	0	4	—	2
39 Schneider	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	—	1
Females Whose Symptoms Arose After the 35th Year																				
40 Belkin	0	0	+	+	+	0	0	+	+	0	0	0	0	0	0	0	0	5	2	4
41 Raskin	0	0	0	0	0	+	0	0	+	0	0	0	0	0	0	0	0	2	4	3
42 Weiner	0	0	+	0	0	0	0	+	+	0	0	0	+	0	+	0	0	7	4	1
43 Kaplowitz	0	+	+	+	0	0	0	+	+	0	0	0	0	+	+	+	0	8	3	4
44 Jandus	0	0	0	0	0	0	0	+	0	0	0	0	0	0	0	0	0	1	1	0
45 Silverstein	+	0	0	0	0	+	0	+	+	0	0	0	0	0	+	0	0	5	3	2
46 Litschstein	0	0	+	+	+	+	0	+	0	+	0	0	0	+	0	0	+	8	3	2
47 Feldman	0	0	0	0	0	+	0	0	0	0	0	0	0	+	+	0	0	3	4	2
48 Glassowitz	0	+	0	0	+	0	0	0	0	0	0	0	0	+	0	0	+	5	—	—
49 Muegelin	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	0
50 Nacht	0	+	+	0	0	+	0	0	0	+	0	0	0	0	0	0	0	5	2	0
51 Sigismund	0	+	+	+	+	+	+	0	+	0	+	+	0	+	0	+	+	10	0	0
Total	6	14	22	20	12	24	16	19	17	8	1	3	7	9	13	6	8			

\* The sympatheticomimetic "score" is obtained by adding the number of symptoms listed. The epinephrin reaction is estimated by the extent of the pressor response (0 = below 12 mm, 1 = 12-15, 2 = 15-20, 3 = 20-25, 4 = over 25), the atropin reaction by the pulse rate variation (0 = below 10 per minute, 1 = 10-15, 2 = 15-20, 3 = 20-25, 4 = over 25). A dash (—) in either column indicates that the test was not done. Note that there is no relationship between "score" and intensity of drug reactions. Compare these symptoms with present symptoms of exophthalmic goiter and with residual symptoms in "arrested" cases.

*Course*—The hospital course was complicated by tonsillitis. Roentgen-ray treatment of the tonsils was started. She went to the country for one month and then remained home at full rest for one month. She has been at work ever since. Despite the illness of her mother and trouble with the landlord, she has been free of symptoms for fifteen months.

**SUMMARY** Psychic insult, exophthalmic goiter, recovery from first crisis, interval hemithyroidectomy, second crisis, partial thyroidectomy, third crisis, spontaneous recovery, well now for more than a year and doing full work.

### ETIOLOGY

*Predisposing Factors*—In a small group (10 per cent) of patients no previous symptoms were noted. In 90 per cent of the patients, persistent or recurring symptoms existed. When these were tabulated, the syndrome of autonomic imbalance was again reconstructed (Table 2).

Stern<sup>4</sup> has called attention to the presence of a predisposition. He emphasized, as did Charcot,<sup>5</sup> the incidence of functional nervous disorders in this group. Four of our patients had psychoses, two had epileptic convulsions, and two had hysterical aphonia.

TABLE 3—RESUMÉ OF ETIOLOGY IN CASES STUDIED

Condition *	No. Cases	Per Cent
Psychic insult (alone)	18	35
Psychic insult (associated with other factor)	37	72
Focal infection (tonsils)	14	27
Focal infection (sinuses)	8	16
Focal infection (total)	20	40
Dietary insufficiency	2	4
Sex epoch	4	8
Unknown	9	18

\* Associated conditions are not listed. Direct causal relationship must be demonstrable to warrant inclusion in this table.

The predisposing factors bore no relation to the age of the patient, to the duration, or to the type, of thyroid enlargement.

*Exciting Causes*<sup>6</sup>—By far the most frequent and important exciting cause was psychic insult. In 72 per cent of the histories this was in immediate relationship to the onset of the disease. Focal infection played an exciting rôle in 40 per cent, the focus being present almost constantly in either the tonsils or the sinuses. Alterations in sex life and dietary insufficiency were operative in a small number. In many of the patients more than one exciting factor occurred (Table 3).

### PATHOLOGY

Two complete necropsies were made. In Case 49, in which death was due to cardiac failure following pneumonia and pericarditis, the

<sup>4</sup> Stern. *Jahrb f Psychol* 29 179, 1908.

<sup>5</sup> Charcot. *Clinical Lectures*.

<sup>6</sup> Under this caption we are not discussing the primary cause of the disease.

thyroid gland was colloid. In Case 8, in which death was due to a psychosis associated with the exophthalmic goiter, the summary of the pathologic findings was (1) hyperplasia of the thyroid gland, (2) persistent thymus (weight 20 gm), (3) edema of the lungs, (4) absence of lipid in the sections of the suprarenal, (5) parenchymatous degeneration of the liver.

#### SUBJECTIVE SYMPTOMS

Asthenia (88 per cent), loss of weight (84 per cent), palpitation (84 per cent) and nervousness (80 per cent), were the most frequent symptoms. Of the cardinal symptoms of exophthalmic goiter, goiter was present in 78 per cent, and the subjective presence of exophthalmos was reported in but 60 per cent, and of tremor in 70 per cent. The surprising frequency of dyspnea (62 per cent), vomiting (30 per cent), dysphonia (24 per cent), dysphagia (10 per cent), headache (28 per cent), precordial pain (14 per cent), and pain in the eyes (16 per cent), is worthy of comment.

*Palpitation*—Palpitation bore no constant relation to the heart rate, blood pressure or pulse pressure. It was usually precordial, but at times epigastric. In patients whose symptoms had otherwise been alleviated completely, mental or physical strain sometimes induced sharp attacks of palpitation.

*Diarrhea*—The most characteristic type of diarrhea was the passage of frequent, small stools, but the total daily amount of feces was not excessive. The stools themselves were normal. The diarrhea was unaffected by diet and drugs. The patient might continue to gain weight, even when this symptom was distressing. Its occurrence was much more frequent in the group of older women, of whom seven of twelve suffered from this complaint.

*Dyspnea*—This symptom was present with surprising frequency. It was not associated with either cardiac or pulmonary disease and was not necessarily present in those with the highest metabolism.

*Asthenia*—Asthenia was usually the earliest and most persistent symptom. Of the six patients who did not complain of asthenia, five were males.

*Dysphonia*—In none of the patients who had dysphonia was any abnormality present in the larynx. None of the patients had a substernal goiter. Of the four patients who had substernal goiter, none had hoarseness.

*Dysphagia*—As with the symptom of dysphonia, no mechanical reasons could be found for this symptom.

*Edema of the Feet*—This symptom occurred five times. In one woman it was due to varicose veins, in the others no static, circulatory or renal cause was present.

TABLE 4—OBJECTIVE SIGNS AND LABORATORY DATA IN EXOPHTHALMIC GOITER \*

	Pulse Rate	Systolic Blood Pressure	Pulse Pressure (Actual)	Pulse Pressure (Per Cent)	Transverse Diameter of Heart	Locomotion Pulse	Palpable Spleen	Lymphadenopathy	Palpable Liver	Tremor (Coarse or Fine)	Mydriasis	Exophthalmometer	Neck Circumference	Consistency (Firm or Soft)	Uniform or Discrete Tumor	Bruit	Substernal	Lymphocytes (Actual)	Lymphocytes (Per Cent)	Cholesterolin	Sugar (Fasting)	Sugar (After Glucose)	Basal Metabolism (entrance)
1	104	170	67	51	75	0	0	0	0	0	+	20	32	T	U	0	0	2,000	47	148	115	180	37
2	100	162	62	52	72	0	0	0	0	0	+	31	37	T	U	0	0	3,300	28	114	120	130	46
3	100	128	55	55	72	0	0	0	0	0	+	31	38	T	U	0	0	3,100	45	266	107	—	26
4	100	200	100	50	111	0	0	0	0	0	+	27	27	T	U	0	+	2,600	35	—	112	140	46
5	90	132	61	48	59	0	0	0	0	0	0	18	34	T	U	0	0	2,200	42	150	128	340	39
6	92	118	50	59	77	0	0	0	0	0	0	21	36	T	U	+	0	3,000	60	—	90	120	54
7	120	117	37	32	77	0	0	0	0	0	0	22	37	T	U	+	0	2,200	22	90	130	140	35
8	120	164	88	54	77	0	0	0	0	0	+	18	38	T	U	+	0	1,840	28	116	128	380	75
9	80	—	—	—	—	0	0	0	0	0	0	—	—	T	U	?	?	—	—	—	—	—	—
10	100	138	70	51	77	0	0	0	0	0	+	21	35	T	U	+	0	2,150	43	—	132	—	38
11	100	142	100	—	77	0	0	0	0	0	0	21	31	T	U	+	0	5,400	40	92	210	—	8
12	170	114	—	—	77	0	0	0	0	0	0	23	34	T	UD	+	0	2,600	28	107	100	108	25
13	120	120	50	42	18	0	0	0	0	0	0	19	35	T	U	+	0	3,700	33	138	180	170	40
14	90	124	—	53	77	0	0	0	0	0	0	22	32	T	U	+	0	3,500	15	230	106	—	44
15	112	124	—	—	77	0	0	0	0	0	0	26	32	T	U	+	0	2,200	31	—	113	180	53
16	100	—	—	—	77	0	0	0	0	0	0	23	31	T	U	+	0	1,900	20	—	—	—	18
17	140	144	82	58	12	0	0	0	0	0	0	28	32	T	U	+	0	3,840	60	132	130	—	58
18	120	140	50	36	77	0	0	0	0	0	+	22	34	T	U	+	+	3,850	35	90	90	—	57
19	100	96	96	100	77	0	0	0	0	0	0	21	33	T	U	+	0	—	—	—	100	—	24
20	120	140	50	36	77	0	0	0	0	0	0	19	29	T	U	+	0	—	37	—	130	100	35
21	84	110	45	41	77	0	0	0	0	0	0	25	34	T	U	+	0	1,500	38	176	130	138	55
22	110	120	50	38	77	0	0	0	0	0	0	21	35	T	U	+	0	1,400	26	—	—	—	40
23	100	140	80	62	77	0	0	0	0	0	0	21	30	T	U	+	0	1,900	24	120	110	140	20
24	108	144	61	44	77	0	0	0	0	0	0	19	30	T	UD	+	0	1,800	50	—	—	—	17
25	120	132	78	60	77	0	0	0	0	0	0	19	36	T	U	+	0	2,800	35	—	90	170	34
26	90	—	—	—	77	0	0	0	0	0	0	23	33	T	U	+	0	2,900	34	—	116	—	29
27	100	130	70	55	12	0	0	0	0	0	0	17	36	T	U	+	0	2,100	30	—	—	—	48
28	152	120	70	55	18	0	0	0	0	0	0	17	36	T	U	+	0	2,800	36	114	110	—	64
29	120	—	—	—	77	0	0	0	0	0	0	—	—	T	U	+	0	—	—	—	—	—	100
30	136	138	52	—	77	0	0	0	0	0	0	23	34	T	U	+	0	—	—	—	—	—	64
31	100	112	50	46	77	0	0	0	0	0	0	20	34	T	U	+	0	3,600	41	—	—	—	58
32	100	138	50	43	16	0	0	0	0	0	0	30	33	T	U	+	0	9,700	61	—	—	—	50
33	100	108	64	59	77	0	0	0	0	0	0	18	N	T	U	0	0	2,000	27	130	110	108	40
34	120	106	56	52	77	0	0	0	0	0	0	17	31	T	U	0	0	2,800	52	—	107	129	36
35	110	118	46	39	77	0	0	0	0	0	0	37	37	T	U	+	0	2,300	30	136	104	113	22
36	12	131	84	62	77	0	0	0	0	0	0	18	N	T	U	0	0	1,600	28	—	100	160	48
37	84	140	95	73	16	0	0	0	0	0	0	27	38	T	U	+	0	4,400	35	—	115	150	35
38	120	170	70	46	77	0	0	0	0	0	0	N	N	T	U	+	0	2,850	22	114	60	240	62
39	100	120	40	33	77	0	0	0	0	0	0	—	—	T	U	0	0	—	—	—	—	—	37
40	140	170	70	47	77	0	0	0	0	0	0	N	N	T	U	0	0	2,000	30	—	—	—	30
41	84	110	15	41	77	0	0	0	0	0	0	15	30	T	U	0	0	4,100	50	—	135	250	48
42	120	140	85	60	14	0	0	0	0	0	0	19	33	T	U	+	+	3,200	50	132	115	—	68
43	110	148	68	47	77	0	0	0	0	0	0	18	34	T	U	+	+	1,100	21	—	95	—	47
44	138	97	47	48	77	0	0	0	0	0	0	17	28	T	U	0	0	2,800	35	130	—	—	63
45	90	140	50	36	77	0	0	0	0	0	0	17	28	T	UD	0	0	3,400	50	—	—	—	28
46	120	170	80	47	77	0	0	0	0	0	0	21	27	T	U	0	0	2,600	28	130	85	260	50
47	112	100	65	65	77	0	0	0	0	0	0	18	27	T	DD	+	+	2,250	45	—	140	150	42
48	74	170	70	11	18	0	0	0	0	0	0	N	37	T	DD	0	0	2,700	17	—	—	—	48
49	74	120	70	58	77	0	0	0	0	0	0	14	31	T	UD	0	0	2,100	28	130	78	113	50
50	120	200	200	100	14	0	0	0	0	0	0	17	N	T	U	0	0	3,700	35	—	136	240	57
51	100	160	100	62	77	0	0	0	0	0	0	35	35	T	D	0	+	3,680	40	132	60	240	57

\* Pulse pressures were all above 40 mm Hg and 30 per cent. In older women fine tremor was unusual, exophthalmos usually was below 20 and neck circumference rarely exceeded 30 cm except when there was a large discrete tumor. In younger women, fine tremor was more frequent, exophthalmos usually exceeded 20 and neck circumference was greater than 30 cm, due to diffuse and uniform thyroid enlargement. Bruits was not necessarily present in the severest cases. Lymphocytosis invariably was present but did not parallel the severity of the disease. Cholesterolin usually diminished in amount but not in inverse relation to the basal metabolism elevation. Sugar tolerance test was frequently normal. Basal metabolism and pulse rate were not necessarily elevated correspondingly.

*Pain in the Eyes*—In two of the eight women who complained of this symptom, the exophthalmos was very slight

#### OBJECTIVE SYMPTOMS (TABLE 4)

*Skin and Appendages*—Fifty per cent of the patients presented the scanty eye-brows so characteristic of myxedema. Five patients had a generalized diffuse brown pigmentation. In one of these patients the disease was acute.

*Laryngeal and Rhinologic Findings*—(Drs. Yankauer and Kaempfer). Without exception foci of infection were present in the nose or throat in all cases. Purulent secretion was expressed from the tonsils of all patients, four had hypertrophied lingual tonsils, and five had sinus infection. Activity in these foci, or reinfection, at times caused serious and protracted remissions of the exophthalmic goiter. Surgical drainage of a sinus or tonsillectomy often alleviated the symptoms.

*Tachycardia*—The great difficulty in obtaining a basal pulse rate detracts from the importance of this constant symptom. The lability of the pulse rate is so great that it is practically impossible to obtain a satisfactory norm. Pulse rates taken during sleep often, but not invariably, showed a marked decrease. A comparatively slow pulse was observed with relatively high metabolism (Cases 6, 21, 37 and 45). A marked decrease in metabolism occurred without slowing of the pulse rate (Cases 25, 27, 28 and 31). Digitalis did not alter the tachycardia.

*The Heart*—Twelve patients showed definite enlargement. In none was there an accompanying valvular defect. In three of these cases, the electrocardiogram showed left ventricular preponderance. In two others of this group there was auricular fibrillation.

*Cardiac Sounds*—In many of the patients the snap of the first apical sound and the accompanying thrill simulated closely the signs in mitral stenosis. In only one (Case 27) could we feel sure that a true stenosis existed. Systolic murmurs at the apex and base were common and of no significance.

*Electrocardiogram*—Auricular fibrillation was seen in four patients. In one (Case 45), the attack was transitory during a bronchopneumonia. In Cases 48, 49 and 51 the fibrillation was persistent. In Case 48 quinidin and in Case 51 digitalis, was without effect. All of these women were in the older group and none had substernal thyroids. The absence of left ventricular preponderance in the majority of patients with cardiac enlargement was thought to indicate a concentric hypertrophy.

*Blood Pressure*—Cases 2 and 50 had a definite hypertension in the absence of cardio renal disease. Lability of the blood pressure was striking, the systolic pressure varying between 140 and 220 mm of mercury.

*Pulse Pressure*—In every instance the pulse pressure was distinctly increased, both on an absolute and a percentile basis. Diastolic pressure was low in all, and in three patients (Cases 11, 19 and 30) the sounds could be heard at zero. This was a temporary phenomenon. In none of these patients was aortic disease present.

*Spleen and Superficial Lymph Nodes*—The associated enlargement of these structures was surprisingly frequent. In none of the patients was there any obvious explanation for the adenopathy. In acute febrile cases the enlargements were frequent and often painful. In one patient (Case 30) these organs enlarged strikingly as the result of an epinephrin reaction.

*Tremor*—The rapid fine tremor of exophthalmic goiter was no more frequent than a coarse, slow, irregular tremor. The latter was encountered particularly in the group of older women.

*Exophthalmos*—The relationship between the presence of exophthalmos and the age of the women at the onset of the disease as noted by Trousseau<sup>7</sup> was confirmed. In the younger group of patients, who developed their illness before the age of 35, the bulging was striking and was rarely below 20 mm. In the older group, exophthalmos was frequently absent, and if present was rarely marked, in only one of the twelve women in this group did the measurement exceed 20 mm.

Plummer<sup>8</sup> regards exophthalmos as a most important differential point in the diagnosis of toxic hyperplastic and toxic nonhyperplastic goiters. It is his belief that an alteration in the construction of the thyroxin nucleus determines the production of the exophthalmos. The striking rôle of the age of the patient, as demonstrated above, indicates that it is a change occurring in the end organs rather than an alteration in the thyroid structure or secretion that determines the presence of this symptom. The degree of the exophthalmos does not parallel the severity or progress of the disease.

Exophthalmos is not pathognomonic and can be observed in otherwise normal patients and in those with autonomic imbalance.<sup>1</sup>

*Ocular Manifestations*—(Dis Schlivek, Wolff, Barnett and Tenner). The ocular manifestations seem to have been greatly over-emphasized.<sup>9</sup> Any or all of the classical signs may be present in normal people or in those with autonomic imbalance. Furthermore, these signs

7 Trousseau. Clinical Lectures, published by the Sydenham Society.

8 Plummer. Tr. A. Am. Phys., 1916, p. 138.

9 Sattler. Die Basedowische Krankheit, Engelmann, 1909.



are transitory. Aside from the exophthalmometer readings, the most valuable sign in our experience has been the locomotion pulse of the vessels in the fundus oculi.

*Goiter*—Fourteen per cent of the patients had a thyroid gland that was visibly and palpably normal. A normal or very slightly enlarged gland was the rule in the group of the older women. The consistency of the glands varied. Six patients presented enlargements that were due to discrete nodules within the substance of the gland, presumably either cysts or adenomas. Two of these six patients (Cases 12 and 24), both younger women, had exophthalmos. The remaining four (Cases 45, 48, 49 and 51) of the older women had no exophthalmos. Eight patients had substernal goiters, none of these had pressure manifestations. Thrills, bruits and murmurs were present over the gland in twenty patients, the presence or absence of these bore no relation to the severity of the disease. "Goiterophobia" was the cause of unusual mental distress in many of the patients.

*Anthropologic Make-Up*—We did not constantly encounter the thyroidal "type" of the endocrinologists. Many of the patients were of the thyroid habitus, as many had the characteristics of the other so-called "endocrine types." That this was due to associated involvement of other endocrine glands seems a rather poorly constituted biologic argument.

*The Liver*—In both patients who came to necropsy the liver was extremely small, though in neither was there cirrhosis<sup>10</sup>.

*Fever*—In the acute cases and in acute exacerbations fever was present. When it accompanied psychoses it was of serious prognostic omen.

*Loss of Weight*—The weight usually furnished an excellent index of the progress of the disease. Maintenance of weight or tendency to gain was a favorable prognostic index. The gain of weight was often quite extraordinary, and might proceed in spite of a constantly and greatly elevated metabolism (Cases 29 and 51).

*The Endocrine System*—The problem of polyglandular involvement is so difficult of approach that we shall limit ourselves to a discussion of clinical findings. The observations on the thyroid have been mentioned previously. At the necropsy in Case 8 a persistent thymus and a diminished suprarenal cortex were found. This patient also had atrophic testes, but the atrophy was no more marked here than in the other parenchymatous organs. Menstrual irregularities were definitely associated with the disease in eight patients. The type of the disturbance was not constant and the pelvic contents were normal.

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<sup>10</sup> Marine, David. Bull. Johns Hopkins Hosp. 28:359, 1907.

*Hematologic Findings*—The hemoglobin and red cells were normal. In all but three patients there was a relative and absolute lymphocytosis. There was no definite relationship between the severity of the disease and the degree of lymphocytosis.

*Metabolism*—The blood constituents showed no constant alteration. The nitrogenous products were normal except in Case 8 at the time of the febrile psychosis, when, in the face of normal renal function, the values rose considerably. The increase consequently was a catabolic phenomenon. Except for the increase in this same patient, the uric acid and creatinin values were normal. With one exception all of the patients had a blood cholesterol well below the upper limit of normal. The diminution in the cholesterol content was no accurate index of the severity of the disease. Sugar tolerance<sup>11</sup> tests were made on twenty-seven patients, in nine the return to normal was obtained within two hours. This test, consequently, was not sufficiently constant to be a reliable diagnostic sign.

The oxygen consumption was determined in the estimations of basal metabolism. To establish the diagnosis of exophthalmic goiter in clearly defined cases, such as these, the basal metabolism is of little value. In another place<sup>1</sup> we have discussed its crucial value, however, in the exclusion from the group of exophthalmic goiter of patients with autonomic imbalance. We have arbitrarily chosen to accept the basal metabolism as the best available objective diagnostic sign<sup>12</sup>. For the present we do not accept as exophthalmic goiter a case in which there is not, or has not been, a constant and distinct elevation of the basal metabolism. For the estimation of the progress of the disease it is unquestionably the best objective index<sup>13</sup>. There are, however, striking exceptions to this, and patients may have severe manifestations of the disease and a slight elevation of metabolism (Case 3), or they may be progressing favorably and the metabolic elevation (Case 29) persist unchanged.

We have included one patient (Case 11), whose metabolism was never above  $+8$ . This girl was 13 years of age, her height was 66 inches and her weight 135 pounds. Her oxygen consumption was distinctly elevated, but the normal figures for her age brought her basal metabolism within normal limits. In view of the clinical findings in this patient, we were compelled to ignore the metabolic test.

*Drug Reactions*—In Table 5 will be found the results of the atropin and epinephrin tests. Two patients (Cases 12 and 13) did not respond to epinephrin. There was no constant relationship between the pressor

11 Janney and Henderson. Arch. Int. Med. **26**: 297 (Sept.) 1920.

12 DuBois. Arch. Int. Med. **17**: 915 (June) 1916. Means and Aub. Arch. Int. Med. **24**: 645 (Nov.) 1919.

13 Means and Aub. J. A. M. A. **69**: 33, 1917.

and accelerator reactions, nor between the circulatory response and the subjective or objective symptoms. The severity of the epinephrin reaction may be so great as to be alarming. The drug should never be administered at the height of the disease, and a preliminary injection, not exceeding 0.2 or 0.3 c.c. should be made.

The atropin response was absent in only 24 per cent of the patients tested. It bore no relation to the epinephrin response, to the symptoms

TABLE 5—RESPONSES OF PATIENTS WITH EXOPHTHALMIC GOITER TO EPINEPHRIN AND ATROPIN INJECTIONS

Name	Before Epinephrin		After Epinephrin		Minims Epinephrin Used	Pulse	
	Pulse	Blood Pressure	Pulse	Blood Pressure		Before Atropin	After Atropin
Albeck	110	120	116*	142*	5		
Albert						102	132*
Belford						78	120*
Belkin	96	120	104*	138*	5	76	128*
Berkowitz	100	114	122	118	5	100	130*
F. Cohen	108	126	114*	152*	5	100	140*
Dunkelman	120	136	148*	156*	7	114	132*
Droga	128	120	136	126	5		
Faber	106	110	130*	150*	3	104	120*
Feidman	110	120	204* (?)	184*	7	112	126*
Fox	72	110	108*	138*	7	80	106*
Fisher		126		178*	3	108	128*
Goldstein	130	138	156*	180*	3		
Green		96		160*	7	108	132*
Griffith	106	114	118*	198*	5	106	110
Hamburger						112	120
Handel	100	104	120*	160*	5	108	104
Hoffman	93	94	116*	138*	5	104	108
Honig	80	104	96*	142*	5	80	106*
Jandus	124	130	128*	154*	5	124	134*
Kaplowitz	116	122	132*	160*	7	120	132*
Kraft	104	106	124*	160*	5	104	132*
Litsehstein	110	160	120*	188*	3	120	148*
Maegelin						108	184*
Nachit	120	170	124*	192*	7	120	120
Nalmon	96	130	120*	160*	5	92	118*
Preisler	126	124	138*	170*	5	112	138*
Raskin	83	104	112*	188*	5	84	106*
Rodamon	70	124	70*	170*	4	120	156*
Rosenthal	120	130	132*	150*	2	116	164*
Sigismund	92	134	100*	146*	7	102	100
Silverstein						96	122*
Spiegel						130	142*
Tanguai	100	108	100*	126*	7	112	140*
Welner	100	130	136*	154*	7	112	134*
Weistein	90	100	100*	112*	5	90	74
Woliman	106	114	120*	140*	6	112	116

\* Positive response

Recapitulation. Of 34 patients tested with atropin, 26 reacted, or 76 per cent, of 31 patients tested with epinephrin, 29 reacted, or 93 per cent.

or to the severity of the disease. The initial vagus center action was usually present and bore no relation to the epinephrin response. It should again be emphasized that both these reactions may occur in normal persons, and particularly in patients with autonomic imbalance.

The interpretation of the sensitiveness to epinephrin has recently come in for a great deal of comment<sup>14</sup>. We have shown that sensitization to epinephrin may occur in the complete absence of the thyroid

gland, and that the alleged synergism between thyroxin and epinephrin and the alleged action of thyroxin on the involuntary nervous system are based on an erroneous interpretation of laboratory data

The subjective manifestations resulting from the epinephrin injection closely mimicked the original complaints of the patients

*Psychic*—These patients were characteristically sensitive, restless and emotionally unstable. Four patients had true psychoses, in two of these, death occurred. When the psychosis is associated with fever, the prognosis is particularly poor

#### TYPES OF DISEASE

Two factors were revealed as determinants in the clinical variety of the manifestations of the disease. Of these, the first was the existence of the predisposition (autonomic imbalance). Its importance lay in the fact that the prognosis in patients with predisposition must include the statement that complete symptomatic recovery could not be anticipated. The best that therapy can afford is a restitution to autonomic imbalance with the persistence of these residual symptoms. The second and more important factor in determining the type was the age of the patient at the onset of the disease. It was noted (Table 4) that in the older group of women exophthalmos was comparatively infrequent and rarely measured more than 20 mm, the goiter was rarely large, except when the enlargement was due to a discrete tumor within the gland. The drug reactions in this older group were rarely intense (Tables 2 and 5), a fine tremor was seldom encountered but auricular fibrillation and diarrhea were much more frequent than in the younger group. Of the classical symptoms of exophthalmic goiter in women whose disease began after their thirty-fifth year, tachycardia alone was constant—the exophthalmos, diffuse hypertrophy of the thyroid and the tremor being more frequently absent. The basal metabolism estimation in this group, fortunately, was usually high and out of proportion to the clinical manifestations. We<sup>1</sup> have called attention to the frequent occurrence of the cardinal symptoms of exophthalmic goiter in patients who have no elevation of the basal metabolism. To this syndrome we have applied the name autonomic imbalance, and it is differentiated objectively solely by the basal metabolism estimation.

Other attempts to subgroup our patients were essayed and abandoned. Division into sympathotonic and vagotonic groups<sup>15</sup> based on drug reactions was not clearly defined. A subgrouping on an anatomic basis, as suggested by Plummer,<sup>7</sup> did not hold. Plummer subgrouped his patient into toxic nonhyperplastic and toxic hyperplastic, using as criteria the duration of the thyroid tumor before the onset of symp-

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15 Eppinger and Hess. *Vagotonia, Nerv & Ment Dis*, 1917, Monograph 20

toms, its histologic appearance and the presence of exophthalmos. While no histologic material is available in our cases, the subdivision according to the presence or absence of exophthalmos seemed usually related to the age of the patient and independent of the nature of the thyroid enlargement or its duration.

#### MANAGEMENT

The patients were placed under as nearly ideal hygienic and psychic conditions as is possible in the wards of a large general hospital. A high caloric diet was ordered (about 3,000 calories). Both nurse and patient were instructed that gain in weight was essential to recovery. Wet packs at 75 F. were given for the symptomatic relief of restlessness, insomnia and sweating. In many patients, colon irrigations were given without any definite rationale and without any definite amelioration of symptoms. Phenobarbital (luminal), 1½ grains, was used as a hypnotic. Aside from iodine (syrup of ferrous iodide), given to reduce the neck circumference,<sup>16</sup> no other drug was generally employed.

By means of the sequential history, the confidence of the patient was won and a definite exciting cause, usually psychic or infectious, revealed. When a direct exciting relationship to focal infection was demonstrable, surgery was resorted to, with results that were occasionally excellent.

The patients were told that operation would not be necessary and that an attempt would be made to restore them to economic usefulness, though a few of their symptoms might persist. On discharge, they were warned that they were to regard themselves not as cured, but in an arrested condition and that it was necessary for them to take particular care of themselves and for their families to take particular care of them, without coddling. The demonstration to the active patients of those whose disease was arrested was a therapeutic boon.

Only one specific therapeutic endeavor is recorded. In two patients (Cases 6 and 14) an acute exacerbation of symptoms, accompanied by fever (febrile crisis), occurred. Intravenous injection of thyroxin was followed in forty-eight and sixty hours, respectively, by lysis and a striking improvement in the entire clinical picture. The patients had previously seemed to be on the verge of death.

#### COURSE AND PROGNOSIS (TABLE 1)

There was a tendency to recovery in these patients that was gratifying, even astounding, and to which, at present, we are inclined to attribute many, if not most, of the so-called cures. As a rule, the patients were kept in bed for from six to ten weeks. Of the sub-

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<sup>16</sup> Marine, David and Kimball, O. P. Prevention of Simple Goiter in Man, *Arch. Int. Med.* 25:661 (June) 1920.

jective symptoms, asthenia and palpitation persisted most constantly. The other symptoms were usually alleviated. Of the objective manifestations, the goiter, exophthalmos and basal metabolism elevation persisted, but were distinctly lessened.

The patients were then sent to the country for a month. The majority of the women went to the Loeb Home, where the intelligent cooperation of Mrs. Israel, the superintendent, did much to secure for them the mental and physical rest they so greatly needed. Most marked, during this period was the large gain in weight. Further diminution in the symptoms occurred, and at the end of that time economic restitution was possible, though symptomatic cure seldom occurred.

Exacerbations occurred several times, always subsequent to a tremendous psychic trauma or an acute infection, usually tonsillitis or sinusitis. One patient (Case 6) had a true recurrence following overwork and acute tonsillitis. Practically all of the patients have been observed for more than a year and are still under our care.

Several additional clinical points are to be observed in rendering a prognosis. (1) After the fiftieth year, the prognosis is poor. (2) Complete recovery should never be expected, especially in those patients who have had a previous autonomic imbalance. (3) Those patients with many symptoms and a slight metabolic elevation often run a protracted course. (4) A catabolic accumulation of products in the blood is of evil omen. (5) Similarly, with a febrile crisis or psychosis, the outlook is precarious. (6) Favorable indications are gain in weight, acute onset in a previously healthy person, social and economic freedom, and the presence of sufficient ignorance on the part of the patient to insure strict obedience, or sufficient intelligence to insure helpful cooperation.

#### DISCUSSION OF RESULTS

*Fatal Cases*—Five patients died. Of these, one died as the result of a hemorrhage from a gastric carcinoma and another died from cardiac failure following pyelitis, pneumonia and pericarditis. Two deaths were directly due to the exophthalmic goiter. Of these, one patient (Case 38) was observed by us only two days. She was admitted with a febrile psychosis and it was necessary to transfer her to the psychopathic ward at Bellevue Hospital, where she died later. The other patient (Case 9) died in our wards with a febrile psychosis and an intense accumulation of catabolic products in the blood stream. The fifth death occurred in a young girl (Case 14) during her convalescence. This was a *status death*. She had been admitted to the hospital with a febrile psychosis. After a febrile period of three weeks, thyroxin, 3 mg., intravenously, was followed in forty-eight hours by lysis and complete recovery. She was sent to the convalescent home,

and there, after a few weeks of steady improvement, experienced headaches. While suffering one of these, she had a convulsion and died. Necropsy revealed the findings typical of status and nothing else. This patient had had a subtotal thyroidectomy in Russia seven years previously.

*Failures*—Two cases are reported as complete failures. One patient (Case 19) has been lost from sight, but we feel that she would have kept in communication with us had her condition been satisfactory (This patient since reports herself as economically restored). The second failure was in a woman, aged 53, with auricular fibrillation and persistent diarrhea (Case 50). Surgical intervention was suggested, but the surgeons did not regard her as a sufficiently safe risk to attempt operative interference.

*Remissions*—One man (Case 6) had a real remission following overwork and an acute tonsillitis. He had been well for one year previously.

*Economic and Social Incapacity*—(Table 1). Three patients are still economically incapacitated. Of these, one (Case 51) is still suffering sufficiently from her disease to make her useless socially. She has improved, however, and is still improving steadily. The other two patients who are incapacitated (Cases 46 and 48) have both improved greatly as far as the symptoms referable to the exophthalmic goiter are concerned, but the former has suffered an acute hydrops of the gallbladder, and the latter is decompensated as the result of auricular fibrillation. It will be observed that one of the two failures and the three women who are still incapacitated are the oldest members of the group.

*Return to Economic Status*—(Table 1). Forty-one, or 82 per cent, of these patients have been socially or economically restored. Of these, twenty-seven, or 54 per cent, were restored within four months, and four, or thirty-one patients all told, within six months of their hospital entry. The protracted recoveries were almost invariably complicated by some other factor, such as sinusitis, pregnancy or continued psychic trauma. Four of these female patients have successfully completed pregnancies.

These forty-one patients, together with the three who, though still incapacitated, are yet making strides toward recovery, make forty-four patients in whom the spontaneous course of the disease has been toward recovery on an economic basis. In the large majority of cases economic restitution may be anticipated within six months, and in a fair majority within four months. In but one of these patients, the majority of whom have been followed now for a year or more, has a true remission occurred.

It should again be emphasized that we refer here to economic recovery. Symptomatic recovery does not occur completely in these patients. Palpitation and tachycardia on exertion, a certain degree of thyroid enlargement and exophthalmos, do not completely and permanently disappear in any case. These patients are not cured, but their disease is in a stage of arrest. This report, furthermore, is not final. These patients are still under observation and will be maintained so indefinitely. This report is inclusive up to June, 1922.

Nevertheless, the restoration of forty-four of fifty patients to economic recovery in so short a time is sufficient to emphasize pointedly the tendency of this disease to spontaneous arrest in the vast majority of instances.

#### BASAL METABOLISM AS INDEX OF PROGRESS

In addition to the use of the social and economic restitution as an index of the course of the illness in these patients, we have followed the basal metabolism. This is beyond doubt the most useful objective criterion with which to estimate the course and end result in exophthalmic goiter. Of the fifty-one patients recorded we have satisfactory data of forty-five. Six patients did not have a sufficient number of readings. Among these were four fatal cases, and in the case of the two patients who remained alive (Cases 5 and 10) readings could not be made because of the refusal of the patients to submit to further tests. Both of these patients, however, are progressing favorably and have been at work for the past few months. Of the forty-five on whom sufficient data are available, thirty-two, or 71 per cent, (Table 1) at present have a basal metabolism of less than plus 18 per cent. Of these, twenty-one had fallen to below plus 18 per cent within four months. Five other patients have fallen to below plus 25 per cent. In other words, thirty-seven of the forty-five patients, or 82 per cent, have fallen to below plus 25 per cent, and in the majority of these, the fall has occurred within four months.

Nine patients still have a basal metabolism exceeding 25 per cent. In only one woman has the metabolism risen under observation. This patient (Case 51) is the oldest member of the group, and though her metabolism remains elevated, she is slowly losing her symptoms.

In the one patient in whom a true recurrence was observed (Case 6), the basal metabolism rose. In one patient (Case 13), the metabolism rose with an exacerbation. Temporary elevations were observed also in seven other patients. These were all definitely associated with the presence of conditions other than active exophthalmic goiter, such as acute gastro-enteritis, sinus infection, pregnancy, psychic insult. All of these causes will be recognized as exciting factors in exophthalmic goiter and emphasize the necessity of maintaining the closest scrutiny over these patients far into their convalescence.



The correspondence of the restitution to economic usefulness, and the fall in the basal metabolism is very striking. There are, however, a few notable exceptions in which economic restitution occurred without a fall in the basal metabolism. Thus one patient (Case 17) was able to do her housework and be symptom free with a basal metabolism of plus 52 per cent on repeated examinations. Furthermore, this woman gained weight even with this elevated metabolic cadence.

The fact that a striking and persistent fall in basal metabolism occurs in the vast majority of these patients, that this fall persists in the majority of them, even under the most adverse social and economic conditions, must serve to indicate strongly that there is in this disease a marked tendency toward restitution to normal, in patients who receive no specific therapy ("spontaneous course").

The use of the figures obtained in this group of patients when plotted should serve to act as a valuable index in the evaluation of specific therapeutic procedures.<sup>17</sup>

#### CONCLUSIONS

1 A careful study of the course of fifty patients suffering from exophthalmic goiter is presented.

2 An attempt was made to ascertain the natural or spontaneous course of the disease. While this could not be accomplished, at least no "specific" measures were attempted.

3 Special care was taken to follow these patients after their discharge from the hospital, and attempts will be made to continue to maintain these patients under observation.

4 The disease seems often to develop on the basis of a diathesis (autonomic imbalance).

5 Focal infection, sex epochs and psychic insult are frequent exciting causes.

6 Pathologic studies usually reveal a universal cellular involvement. Thyroid hyperplasia is neither specific nor constant in the findings, and only by unmerited inferences can a fundamental etiologic rôle be ascribed to the alleged hyperthyroidism that supposedly accompanies hyperplasia.

7 Variation in the clinical picture was not due to alteration in the thyroid architecture. Adenoma may be seen with any type of disease. Only by unmerited inferences can a fundamental etiologic rôle be ascribed to adenomas or to their supposed increased or toxic secretion.

8 The symptoms of exophthalmic goiter are almost all sympathomimetic.

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17 Kessel, Leo, Lieb, C. C. and Hyman, H. T. A Study of Exophthalmic Goiter and the Involuntary Nervous System, IX. An Estimation of the Pathogenesis and the Evaluation of Therapeutic Procedures in Exophthalmic Goiter, *J. A. M. A.* 79:1213 (Oct. 7) 1922.

9 The fully developed syndrome is marked by an elevated metabolic cadence as best measured by the basal metabolism. By this alone can this disease be differentiated from autonomic imbalance. In the stage of arrest, differentiation can be made only by the history of the crisis.

10 The clinical picture varies as the age of the patient at the time of onset of the disease. In other words, the variation, especially in regard to the presence and extent of the exophthalmos, is dependent on the end tissues of the patient, rather than on the specific elaboration of any toxic product.

11 In women who develop the disease after the thirty-fifth year, exophthalmos is mild, if present at all, diffuse enlargement of the thyroid is more often absent than present, hoarseness and fine tremor are rare, and diffuse pigmentation, diarrhea and auricular fibrillation are comparatively frequent.

12 Complete restitution to the normal rarely, if ever, occurs. Exophthalmos, thyroid enlargement, lability of the pulse rate and the sympathomimetic symptoms do not entirely and permanently disappear.

13 A response to atropin and epinephrin, injected subcutaneously, is usually, but not invariably, obtained. Epinephrin sensitiveness has nothing whatever to do with thyroid function.

14 The spontaneous course of exophthalmic goiter is toward arrest in the vast majority of cases. In patients who develop the disease late in life (after 45 or 50) the prognosis is poor. If these cases be excepted, the prognosis is excellent under a regimen of "skillful neglect."

15 To establish the efficacy of any specific therapeutic measure, one should demand that definite proof be offered that the results obtained are better than those reported here of the "spontaneous" course of the disease.

16 Until a specific diagnostic test is discovered, no reported case of exophthalmic goiter should be accepted as a genuine case unless the basal metabolism is distinctly and repeatedly elevated.

#### GENERAL CONCLUSIONS (ARTICLES I-IX)<sup>18</sup>

1 Thyroid hyperplasia and thyroid adenoma may exist for years without at any time causing sympathomimetic symptoms or alteration in metabolism.

2 Disturbances of the involuntary nervous system clinically occur frequently (autonomic imbalance).

3 Such disturbances are usually not attended by metabolic elevation.

4 While these clinical manifestations of disturbances of the involuntary nervous system (autonomic imbalance) are often associated with

<sup>18</sup> I-II, *Am J M Sc* **165**, March, 1923, III, *Arch Int Med* **31**, March, 1923, IV-VII, *Am J Physiol* **63** 60, 68, 83, 88 (Dec.) 1922, VIII, *J A M A* **79** 1099 (Sept. 30) 1922, IX, *J A M A* **79** 1213 (Oct. 7) 1922.

thyroid hyperplasia, there is no reason to believe that the thyroid enlargement is causative and many reasons for thinking that it is secondary and symptomatic

5 In exophthalmic goiter the dominant derangement is in the realm of the involuntary nervous system. This may not be primary, but the primary cause, whatever it be, must at least operate through the mediation of the involuntary nervous system

6 The primary cause of exophthalmic goiter must be sympathomimetic

7 There is a close relationship between exophthalmic goiter and autonomic imbalance. The latter usually presages the former, and is probably a stage in its development

8 Evidence is presented to show that thyroxin is not sympathomimetic either directly or indirectly through synergism with epinephrin even if it be granted that epinephrin controls the involuntary nervous system either in the tonic state or in emergency<sup>19</sup>

There is a marked tendency in patients with exophthalmic goiter to recover spontaneously. This factor must be carefully considered in evaluating "specific" therapeutic procedures

Miss Grace Mayer has acted as volunteer secretary since the beginning of this work. She has kept the records, arranged the files, kept in communication with the patients and assumed all the burdensome details pertaining to the publication. It is in no perfunctory spirit that we acknowledge our appreciation to her for her unflagging effort, her conscientiousness and her intelligent cooperation

We wish to express our appreciation to Miss N. C. Bragaw, medical supervisor, for her unusual assistance in caring for these patients

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19 Lieb, C. C. and Hyman, H. F. *Am J Physiol* 63: 68, 83 (Dec.) 1922

## FURTHER OBSERVATIONS ON THE USE OF A HIGH FAT DIET IN THE TREATMENT OF DIABETES MELLITUS

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### INTRODUCTION

During the early part of this century it was customary to use a very liberal protein fat diet in the treatment of diabetes mellitus. This type of diet was characterized by its high protein content, its relative poverty of carbohydrate and its high caloric value. Mild diabetics did quite well on such a regimen, but the more severely ill patients did not tolerate it without glycosuria and the persistence of diabetic symptoms, and as pointed out by Joslin, coma was so common that the percentage of deaths in hospitals was greater than in homes. It was necessary to conceive of a mysterious "spontaneous downward progress" to explain the constant loss of tolerance in these cases, and the majority of physicians felt that treatment of the severe cases was a waste of time and energy. This type of diet is not by any means without its supporters today, and it is surprising to note how many patients coming to the University Hospital have had their carbohydrate intake strictly limited, but have been allowed to eat as much other food as they wanted, chiefly in the form of meat, eggs and patent diabetic foods.

In 1914 Allen introduced the principle of undernutrition with the object of relieving the strain on the pancreas, and of stopping the spontaneous progress of the disease. In more or less modified form this principle has since then been used widely in the treatment of diabetes mellitus. Under the leadership of Joslin it has been applied in practice by beginning treatment with fasting, which may or may not be preceded by three or four days of observation and increasing curtailment of the diet. After the period of fasting, the diet is built up step by step until the patient is receiving a ration well within his carbohydrate tolerance, in which neither fat nor protein nor carbohydrate furnishes a disproportion of the calories. It is especially insisted that the fat content of the diet be small. The final diet is one which may not and often does not satisfy the caloric requirement of the

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organism. In the more severe cases a marked degree of undernutrition results, with weakness, depression and chronic invalidism, and inanition appears on the records as a cause of death.

There is abundant evidence that overfeeding and large gains in weight are detrimental to the diabetic. On the other hand, a number of very apparent evils are associated with severe undernutrition. It seemed to us possible that a diet could be arranged, which, while still controlling the diabetic state, might avoid the evils of the two extremes. With the basic principles of the metabolism of the three foodstuffs in mind, it is possible, in theory, to construct such a diet by deriving the major portion of the calories from fat. Before advocating the use of such a diet, however, it was necessary to demonstrate that the use of the much feared fat is, in fact, safe.

In a previous communication<sup>1</sup> we reported that in seventy-three consecutive cases this type of diet was strikingly successful in controlling glycosuria, avoiding acidosis, maintaining nitrogen balance and permitting ordinary activity on the part of the patient. In a second communication<sup>2</sup> we showed the beneficial effect of these diets on hyperglycemia. We emphasized the fact, however, that our experience with this diet was brief in relation to the chronicity of the disease, and we were, therefore, very guarded in our statements of the probable results of adherence to it over a long period of time. Nearly two years have elapsed since our first communication, and a statement of the present status of some of our earlier patients and of additional observations on some of our more recent ones cannot fail to be instructive. It is the purpose of this paper to present our experience with the high fat diet in the light of our longer study, and to discuss certain cases which offer striking examples of fundamental principles in the dietetic management of diabetes mellitus.

The diets used are essentially the same as those previously described, more day to day variation in the composition of the diets is allowed than at first in order to relieve the monotony of the menus, but in principle the treatment is the same as that discussed in our first paper. When an adult diabetic patient is admitted to the ward, he is automatically and without preparation given a daily diet which contains protein, from 15 to 20 gm., fat, from 85 to 95 gm., carbohydrate, from 10 to 12 gm. Because of the smaller body mass of children, their total calories are correspondingly reduced, but the proportions of the food stuffs used are

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1 Newburgh, L. H., and Marsh, P. L. Use of a High Fat Diet in the Treatment of Diabetes Mellitus. First Paper, *Arch Int Med* 26:647 (Nov.) 1920.

2 Newburgh, L. H., and Marsh, P. L. Use of a High Fat Diet in the Treatment of Diabetes Mellitus. Second Paper. Blood Sugar, *Arch Int Med* 27:699 (May) 1921.

the same. No preliminary fast or gradation of diets has been used, and the high fat diet is served from the first meal in the hospital. After the adult patient is desugarized, his diet is increased by steps until he is receiving 0.67 gm protein and from 30 to 40 calories per kilogram of body weight, or sometimes a little more than this. In children more protein and more calories per kilogram of body weight are allowed, in accordance with principles that will be discussed later, but the same plan of distribution of the food stuffs is used for children as for adults. In no case in this series has the daily carbohydrate allowance been greater than 35 gm. After the patient has been found to tolerate a maintenance diet of this type during several days in the ward, he is discharged with instructions to adhere to it rigidly.

### RESULTS

Six major considerations enter into a discussion of the dietetic treatment of diabetes mellitus, namely (1) glycosuria, (2) acidosis, (3) nitrogen balance, (4) lipemia, (5) the general condition of the patient, and (6) the effect of treatment on glucose tolerance and expectation of life.

1 *Glycosuria*<sup>3</sup>—Since the first aim of dietetic treatment of diabetes is the avoidance of glycosuria with the associated complications and loss of tolerance, the prime requisite of the diet is that it keep the urine of the diabetic patient free from sugar. We have had the opportunity since the inception of this treatment of observing 190 diabetics. Of these, six entered the hospital in coma or in extremis from other causes, and died either before treatment could be inaugurated or before it could significantly affect the metabolism (Table 12). Eight others remained but a few days, and left against our advice when they found that we had nothing to offer except diet in place of the curative drug or operation that they had expected (Table 13). None of the remaining 176 diabetic patients failed to become sugar free, and all of these were discharged without glycosuria on a maintenance diet. While none of them were "total diabetics," many were of the very severe grades, and a large number of them were young. In Table 1 are presented the ages of onset of this group by decades. Appended is part of the record of one of the younger patients (Case 1).

CASE 1 (22-610)—*History*—A boy, 3 years of age (born Nov. 5, 1918) entered the hospital March 6, 1922, with diabetes that had appeared abruptly in June, 1921, with polyuria and polydipsia. His father's brother has diabetes. There was nothing of importance in his past history. The diagnosis of diabetes was made immediately, and he was taken into a hospital in his home city for treatment, which was instituted with a fast. Little information could be

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<sup>3</sup> No cases diagnosed renal glycosuria are included in this study.

obtained concerning this period of treatment, except that after a few days of fasting his condition seemed very serious and his mother states that he was on the verge of coma. He was given food, but the mother does not know the quantities. His diet was gradually increased until he was receiving protein, 40 gm, fat, 33 gm, carbohydrate 25 gm and 560 calories. On this diet he had constant glycosuria and a heavy ferric chlorid reaction in his urine. During the two months before admission he had not been sugar free at any time. At the beginning of his illness he weighed 32 pounds and at admission 28 pounds.

*Physical Examination*—This showed nothing of importance.

*Comment*—Part of his record is presented in Table 2. It will be noted that his urine became sugar free on the eleventh day and the ferric chlorid reaction was negative at the same time. The gain in body weight during the first few days was probably due to changes in the fluid content of his body. Nitrogen balance was established on a diet containing 30 gm protein, 75 gm fat, and 12 gm carbohydrate. At present, he is receiving 30 gm protein, 115 gm fat, 17 gm carbohydrate and 1,225 calories, which allows him 93 calories per kilogram of body weight. He is slowly gaining in weight and has added one-fourth inch to his height.

TABLE 1—AGE AT ONSET BY DECADES OF AUTHORS' GROUP. FOR COMPARISON A SIMILAR TABLE OF A GROUP OF JOSLIN'S PATIENTS IS ADDED

Age at Onset	Authors' Series		Joslin's <sup>4</sup> Per Cent
	Number	Per Cent	
0-10	6	3.2	5.3
11-20	14	7.4	8.7
21-30	24	12.6	10.8
31-40	33	17.4	13.8
41-50	37	19.5	24.7
51-60	56	29.5	23.0
61-70	17	8.9	10.1
71-80	3	1.6	3.0

In some cases we have had the opportunity of contrasting in the same patient the results of our diets with the results of other methods of treatment. A number of the patients in this series who had been treated unsuccessfully by high protein diets before coming to us became aglycosuric on our diets. That this would occur is only to be expected, but it must be mentioned because of the widespread use of these high protein diets.

Of still greater interest is the group in which fasting and severe undernutrition have failed to control the glycosuria. The records of two patients (Cases 2 and 3) show clearly that some diabetics who could not be made sugar free by starvation may be made so by a high fat diet yielding about 950 calories.

CASE 2 (21-321)—*History*—An American farmer, 28 years of age, entered the hospital March 1, 1921, complaining of the usual diabetic symptoms. There was no family history of diabetes, except that a 4-year old son of the patient has had an occasional glycosuria. There was nothing of importance in his past history. Polyuria, polydipsia and polyphagia developed in August, 1914, when

<sup>4</sup> Joslin, E. P. Diabetes Mellitus, Oxford Medicine, Oxford University Press 4 153, 1921.

the patient was 21 years old. During the following three months his weight fell from 160 to 113 pounds. Treatment was not started until January, 1915. Four days of complete fasting, followed by several days during which he was allowed green vegetables, and two or three more days of fasting, a total of ten days, rendered his urine sugar free. He was discharged on a diet which allowed him considerable freedom in the kinds of the food stuffs that he ate but which was very much restricted in total calories. During the following two years he felt fairly well most of the time, although he had sugar in his urine frequently. Between the Spring of 1916 and March, 1921, he was free from sugar at no time in spite of the fact that he was fasted on five occasions for periods of from four to ten days. During the month preceding his admission to our ward he suffered from epigastric distress, "heart burn" and nausea. His symptoms were sufficiently severe to make his home physician suspect peptic ulcer. His vision had failed and he was badly constipated.

TABLE 2—PART OF RECORD OF A THREE YEAR OLD DIABETIC (CASE 1)

Date 1922	Diet				Urine			Weight Lbs
	Protein, Gm	Fat, Gm	Carbohy- drate, Gm	Calo- ries	Glucose, Gm	Dia- cetic	Nitrogen, Gm	
3/ 8*	14.3	47.0	4.9	480	++++	++++		28
3/ 9	12.2	41.5	6.6	450	5.4	++++		
3/10	13.3	44.0	5.7	470	4.1	++++		
3/11	12.3	43.0	4.8	405	5.4	+++		
3/12	14.4	47.0	6.4	505	3.0	+++		
3/13	16.5	57.6	8.2	615	Trace	++		
3/14	13.1	59.1	11.3	630	7.3	++		
3/15	13.0	54.0	3.8	555	5.1	—		
3/16	13.1	47.1	6.4	501	6.2	+++		30.5
3/17	9.8	40.7	7.2	435	2.3	+++		
3/18	9.7	40.1	6.4	425	0	0		
3/19	10.8	43.3	7.5	465	0	0		
3/20	10.8	43.3	7.1	460	0	0		
3/21	14.8	46.2	7.1	505	0	0		
3/22	14.8	46.2	7.1	505	0	0		30.5
3/23	13.2	40.0	7.1	440	0	0		
3/23 to 3/29	20.0	45.0	7.0	515	0	0		29.0
3/30 to 4/ 5	25.0	55.0	12.0	645	0	0	9.29	29.0
4/ 6 to 4/ 9	20.0	55.0	12.0	665	0	0	7.52	30.0
4/10 to 4/12†	20.0	65.0	12.0	755	0	0	7.82	30.5
4/13	20.0	75.0	12.0	845	0	0		30.0
4/14	Dietetic error				3.7	0		
4/15 to 4/19	30.0	75.0	12.0	665	0	0		28
4/20 to 5/19	30.0	65.0	12.0	735	0	0	5.21	27
5/20 to 6/ 4	30.0	75.0	12.0	845	0	0	4.48	26.5
6/ 5 to 6/12	30.0	85.0	17.0	955	0	0	3.87	27
6/13 to 6/15	30.0	95.0	17.0	1,045	0	0	3.59	27
6/16 to 6/20	30.0	105.0	17.0	1,135	0	0		28
6/21 to 7/20	20.0	115.0	17.0	1,225‡	0	0		29

\* Blood fat, 1.13 per cent

† Blood fat, 0.89 per cent

‡ 93 calories per kilogram of body weight

*Physical Examination*—On examination it was noted that he was decidedly stuporous and went to sleep while his blood was being taken for the laboratory examinations. Later, he could not remember anything that had happened during the first day he was in the hospital. His breath had a decided acetone odor. His right knee jerk could be obtained only on reinforcement and his left could not be obtained at all. His urine contained a trace of albumin, reduced Fehling's solution and gave a heavy reaction with ferric chlorid. His blood sugar was 0.38 per cent and the carbon dioxide combining power of the blood plasma by the Van Slyke method was 37 volume per cent.

*Comment*—The day to day record of his first two or three weeks, with a summary of the following few weeks in the hospital is presented in Table 3. It will be seen that his urine became sugar free on the twelfth day in the hospital.



CASE 3 (21-1993) —*History*—A Russian housewife, 25 years of age, entered the hospital July 13, 1921, complaining of the usual diabetic symptoms. There was no family history of diabetes and her past history was of no importance. In March, 1920, she had severe attacks of cramps in the legs associated with excessive thirst and polyuria. Other symptoms were failing vision, obstinate constipation and progressive loss of weight. She had no systematic treatment until August 13, 1920, at which time she was fasted for five days and her urine became sugar free. Her diet was increased until she was receiving, protein, 50 gm, fat, 20 gm, carbohydrate, 30 gm, about 500 calories with one fast day each week. From this time until July 1, 1921, she adhered rigidly to this diet, which was prepared by a trained dietitian, with the exception of a short period in January, 1921, when she was allowed one or two slices of bacon a day in addition. At no time during this whole period, except on the last day of her initial fast, was her urine free from sugar, this statement was confirmed by

TABLE 3—PART OF RECORD OF PATIENT (CASE 2) WHO HAD FAILED TO BECOME SUGAR FREE DURING SEVERAL PERIODS OF FASTING

Date, 1921	Diet				Urine			Blood		Weight Lbs
	Pro tein, Gm	Fat, Gm	Carbo hydrate, Gm	Calo ries	Amount, Cc	Glu cose, Gm	Dia cetic	Sugar, %	CO <sub>2</sub> , Vol, %	
3/ 2	19.1	95.4	14.2	990	1,250	43.8	++++	0.38	37	133
3/ 3	22.2	69.0	13.4	865	2,150	56.6	++++			
3/ 4	21.7	94.4	14.8	995	1,650	25.1	++			132
3/ 5	20.8	89.9	13.4	940	2,170	18.1	++			
3/ 6	21.2	89.0	13.4	935	1,925	17.5	++++	0.27	51	134
3/ 7	21.2	89.0	13.4	935	2,350	20.2	+++			
3/ 8	20.5	92.4	14.6	970	2,355	17.5	+++			133
3/ 9	19.1	95.4	14.2	990	2,100	11.9	+++			134
3/10	15.3	99.5	11.0	1,000	1,590	7.8	+++			134
3/11	14.9	101.0	10.5	1,015	1,640	5.6	+++			
3/12	15.2	100.1	11.0	1,005	2,335	0	+++			136
3/13	15.4	100.0	11.3	1,005	1,760	Trace	++	0.13	64	
3/14	15.4	100.0	11.0	1,005	1,895	0	+++			134
3/15	15.4	100.0	11.0	1,005	3,150	0	+++			
3/16	15.4	100.1	11.1	1,005	2,215	0	++	0.13	65	132
3/17	24.8	149.6	15.2	1,505	1,565	0	+			
3/18	26.1	151.1	15.3	1,525	4,370	0	Trace			135
3/19	25.2	150.7	14.2	1,515	3,270	0	Trace			
3/20	26.1	149.7	14.6	1,510	3,190	0	0			132
3/21	24.8	149.6	15.2	1,505	2,200	0	0		75	
3/21 to 3/30	43.0	180.0	15.0	1,850		0	0		66	130
3/31 to 4/4	43.0	200.0	15.0	2,030		0	0		65	
4/5 to 4/20	43.0	220.0	11.0	2,200		0	0		65	

her home physician. July 1, 1921, fasting was again started, and this time four days of complete fasting, followed by five days in which she was allowed "a few" 5 per cent vegetables, failed to render her urine sugar free, and she refused to fast longer. During the few days before she came to us she adhered to the original 500 calory diet.

In February, 1920, she weighed 145 pounds.

*Physical Examination*—The patient was an unusually intelligent woman, 59 inches tall, weighing 100 pounds, with no important abnormalities aside from her laboratory examinations. Part of her record is presented in Table 4.

*Comment*—She was discharged from the hospital on a diet which gave her about 1,400 calories daily, and she has remained sugar free up to the present time, a period of nearly one year.

2 *Acidosis*—A diabetic diet, to be successful, must not precipitate acidosis, and should, in those cases in which acidosis is present, be attended by relief of the acidosis. Since the demonstration of the derivation of acetone bodies from fat, there has developed a wide-spread

fear of the use of fat in the treatment of diabetes. It was, therefore, very important that we study with the greatest care the relation between the amount of fat in our diet and acidosis.

Of the 190 patients with diabetes whom we have had under our care since we have used the high fat diets, six gave us no information as to its effect on acidosis. Four of the latter entered the hospital in diabetic coma, the fifth in coma from sepsis, the sixth in extremis following a therapeutic fast, and none of them were treated dietetically. The other 184 patients include eight who left the hospital against our advice within a week and before they were sugar free, but who were, nevertheless, on the diet during the few days they were in the hospital. In none of these 184 cases did an important acidosis develop. It should

TABLE 4—RECORD FROM CASE 3, IN WHICH FASTING AND SEVERE UNDER-NUTRITION HAD FAILED TO KEEP URINE SUGAR FREE

Date 1921	Average Diet				Urine Sugar, Gm	Ferre Chlorid Reaction	Body Weight, Lbs
	Protein, Gm	Fat Gm	Carbohydrate, Gm	Calories			
7/13					25.5	++++	100
7/14					16.2	+++	
7/15					8.8	+++	
7/16	20.0	85.8	13.1	905	4.0	++	
7/17					0		99
7/18					0	0	
7/19					0	0	
7/20					0	0	95
7/21					0	0	
7/22					0	0	
7/23					0	0	
7/24	28.4	137.4	20.8	1,435	0	0	
7/25					0	0	96
7/26					0	0	
7/27					0	0	

be pointed out, again, that every one of these patients, regardless of age, severity of the diabetes or degree of acidosis was placed on the diet at entrance. Early in the use of the treatment a few patients were given sodium bicarbonate, but this has not been used in any case since July 1, 1920, since which date much more than one half of this series of cases have been treated. A few examples are cited showing the absence of acidosis on the treatment.

CASE 4 (21-678)—*History*—An American clerk, 19 years of age, entered the hospital March 24, 1921, complaining of the usual diabetic symptoms. There was no history of diabetes in the family and nothing of importance in his past history. The disease had developed abruptly fifteen months before, and during the first three months he lost 30 pounds in weight. In spite of severe restriction in his diet there was no improvement in his symptoms. Twelve days before he came to us he was fasted for seven days but he did not know whether he became sugar free. There had been some numbness of his feet and for two months he had had boils on his legs.

*Physical Examination*—Evidence of advanced bilateral pulmonary tuberculosis was found and this complication was confirmed by the roentgenogram and the sputum examination. Part of his data are presented in Table 5.

CASE 5 (21-276) —*History*—An American farmer, 22 years of age, entered the hospital Feb 7, 1921, complaining of polyuria, weakness and loss of weight. A brother died of diabetes at 17. The past history is of no importance. His best weight was 164 pounds just before the onset of his diabetes; his weight at admission was 127. His symptoms appeared abruptly in August, 1920, and the diagnosis was made immediately by his physician. His diet was moderately restricted and he continued to lose weight and strength.

TABLE 5—PART OF RECORD OF CASE 4, SHOWING ABSENCE OF ACIDOSIS IN A YOUNG DIABETIC WITH PULMONARY TUBERCULOSIS

Date	Protein, Gm	Fat, Gm	Carbohydrate, Gm	Calories	Sugar	Ferric Chlorid	Plasma CO <sub>2</sub> , Volume per Cent	Blood Sugar, per Cent
3/24*					+++	++		
3/25	21.7	99.4	14.8	995	+	+	61.4	0.33
3/26	29.1	129.1	21.1	1,320	0	0		
3/27	19.1	95.4	14.2	990	0	0		
3/28	21.2	85.9	13.4	910	0	0	61.7	0.23
3/29	20.2	92.4	14.6	960	0	0		
3/30	30.0	147.1	14.2	1,500	0	0		
3/31	31.7	151.9	15.5	1,535	0	0		
4/ 1	29.9	149.4	14.8	1,525	0	0		
4/ 2	30.2	149.3	14.9	1,525	0	0		
4/ 3	28.8	152.4	14.8	1,545	0	0		
4/ 4	30.3	152.0	14.9	1,550	0	0	63.6	0.16
4/ 5	31.1	180.7	14.2	1,800	0	0		
4/ 6	30.0	179.3	14.2	1,785	0	0		
4/ 7	29.1	178.2	15.0	1,765	0	0		
4/ 8	29.7	180.2	15.3	1,800	0	0	61.7	0.16

\* Admitted in evening

TABLE 6—SHOWING ABSENCE OF ACIDOSIS IN YOUNG DIABETIC ON HIGH FAT DIET (CASE 5)

Date	Diet				Urine		Blood Sugar per Cent	Plasma CO <sub>2</sub> , per Cent
	Protein, Gm	Fat, Gm	Carbohydrate, Gm	Calories	Glucose, Gm	Ferric Chlorid		
2/ 8	18.9	91.2	14.2	935	++++	+++	0.26	62.0
2/ 9	20.6	87.6	14.6	940	24.7	++++	0.18	
2/10	20.4	84.2	12.8	890	13.5	++++		
2/11	21.1	93.9	14.9	900	0	++++		
2/12	20.5	83.7	14.4	890	0	++++		
2/13	21.0	92.0	15.0	970	0	++		
2/14	18.2	91.2	14.3	950	0	Trace	0.20	
2/15	20.6	87.6	14.6	940	0	Trace		61.4
2/16	21.5	80.4	14.6	870	0	0		
2/17	21.3	77.7	12.8	845	0	0		
2/18	20.2	87.3	14.1	935	0	0		56.5
2/19	20.5	83.7	14.4	890	0	0		
2/20	20.6	87.6	14.6	940	0	0		
2/21	21.3	77.7	12.8	845	0	0		
2/22	40.6	153.2	20.6	1,625	0	0		
2/23	39.3	156.5	19.6	1,645	0	0	0.10	53.7
2/24	40.2	153.4	20.3	1,625	0	0		
2/25 to 3/ 1	40.2	152.6	20.6	1,615	0	0	0.13	62.6
3/ 2 to 3/ 7	40.8	152.1	20.6	1,615	0	0	0.12	58.9
3/ 8 to 3/12	40.0	180.3	20.4	1,865	0	0		
3/13 to 3/17	40.0	179.4	20.6	1,815	0	0		65.3
3/18 to 3/20	40.5	200.3	25.0	2,065	0	0		59.8
3/21 to 3/29	40.9	200.2	25.0	2,070	0	0	0.08	65.3
3/30 to 4/ 4	40.6	200.2	25.0	2,065	0	0	0.10	60.7
4/ 5 to 4/ 8	43.1	229.1	25.6	2,340	0	0		61.7

*Physical Examination*—Except for septic tonsils, his physical examination was negative. Part of his record is presented in Table 6.

CASE 6 (21-1021) —*History*—An American farmer, aged 45 years, entered the hospital March 19, 1921, complaining of polyuria and weakness. His mother died at the age of 51 of diabetes mellitus. He had had frequent

urinalyses because of his mother's diabetes, but no sugar was found until December, 1920, about two weeks after the onset of polyuria and weakness. A "carbohydrate free" diet failed to render his urine sugar free, his physician stating that the urine always contained from 3 to 6 per cent of sugar.

*Physical Examination*—Except for pyorrhea alveolaris, his physical examination was negative. His average weight was 155 pounds, at admission he weighed 130 pounds. Part of his record is presented in Table 7.

Not only does acidosis not develop in patients who are living on this diet, but it is a fact that all our patients showing at admission an acidosis short of coma rather promptly lost their acidosis while taking the high fat diet. One such case has already been mentioned in our first communication. Three other striking examples are cited from our more recent experience.

TABLE 7—SHOWING ABSENCE OF ACIDOSIS ON HIGH FAT DIET (CASE 6)

Date, 1921	Average Diet				Urine		Plasma CO <sub>2</sub> , Volume per Cent
	Protein, Gm	Fat, Gm	Carbohydrate Gm	Calories	Sugar	Dia- cetic	
4/7	18	85	15	900	++++	++++	64.5
4/8					++++	++++	
4/9					+++	++++	
4/10					+++	+++	
4/11					++	++	
4/12					+	+	
4/13					0	+	
4/14					0	0	
4/15					0	0	
4/16					0	0	
4/17					0	0	
4/18					0	0	
4/19					0	0	63.5
4/20					0	0	
4/21					0	0	
4/22					0	0	
4/23	28	165	30	1,710	0	0	55.1
4/24					0	0	
4/25					0	0	
4/26					0	0	

Reference to the record of one patient (Case 2) and to Table 3 will show that he entered the hospital with a severe acidosis, which disappeared promptly on a high fat diet.

CASE 7 (22-2159) —*History*—An American painter, 34 years of age, entered the hospital July 6, 1922, with a diabetes which had appeared abruptly in December, 1920, with polydipsia, polyuria and progressively increasing weakness. Three days of fasting rendered his urine sugar free and he was finally able to tolerate a fairly liberal diet. About eight weeks previous to admission he had a lower third molar extracted, infection ensued. There was an immediate return of glycosuria which he was unable to control. For the two weeks before he came to the hospital his diet had not been limited and he had become progressively more drowsy until at admission he was semicomatose. His weight had fallen from an average of 140 pounds to 90 pounds, his entrance weight was 103 pounds.

*Physical Examination*—He was very stuporous and there was hyperpnea of the Kussmaul type. The patellar and Achilles reflexes could not be elicited. His skin had a lemon yellow cast, and numerous xanthomatous lesions were

scattered over his body. At the site of the tooth extraction in the lower right jaw there was evidence of osteomyelitis. His hemoglobin was 66 per cent with 3,210,000 red blood cells and without leukocytosis. His blood plasma was creamy.

*Comment*—The osteomyelitic lesion in the jaw was curetted and he was started on the routine diet. Fluids were forced during the first few days in the ward. In Table 8 will be found data of this period of treatment. There was a rapid improvement in the acidosis, as shown by the disappearance of acidosis, as well as by the laboratory findings. A moderate edema, present at entrance, increased rapidly and explains the great gain in weight.

CASE 8 (21-1392)—*History*—An American merchant, 35 years of age, entered the hospital May 18, 1921, complaining of loss of weight, weakness, polyuria and polydipsia. His symptoms developed abruptly in January, 1918, when he was 32 years of age. Glycosuria was found, and he became sugar free on a rather liberal diet. After a few weeks he was advised to return to a normal diet, symptoms and glycosuria promptly reappeared. He again became sugar free on the liberal diet and adhered to it about a year. During

TABLE 8—PART OF RECORD OF CASE 7 RAPID DISAPPEARANCE OF SEVERE ACIDOSIS ON HIGH FAT DIET

Date, 1922	Diet				Urine		Blood			Weight, Lbs
	Pro tein, Gm	Fat, Gm	Carbo hydrate, Gm	Calo ries	Glu cose, Gm	Dia cetic	Sugar, per Cent	CO <sub>2</sub> , Vol per Cent	Fat, per Cent	
7/7	21.7	85.0	12.6	900	50.3	++++	0.53	34	7.6	103
7/8	21.5	85.8	13.3	910	56.2	++++		38		100
7/9	21.0	86.5	13.2	925	29.4	++				101.5
7/10	21.5	86.6	14.1	935	41.4	++		64		108
7/11	20.4	93.6	13.5	980	17.5	+				115.5
7/12	21.3	88.7	13.0	930	11.1	+			2.8	116.0
7/13	20.1	93.7	13.0	975	11.4	0				117.0
7/14	21.7	87.1	12.6	920	Trace	0				116.5
7/15	21.0	86.6	13.2	910	4.0	0				117.5
7/16	21.5	85.8	13.3	910	0	0	0.20		1.69	117.0
7/17	21.7	84.0	14.1	900	0	0		72		119.0

the following year he increased his food intake and frequently found sugar in his urine. During this second year of his diabetes he had frequent night sweats, with one attack of pain in the lower left chest lasting some weeks. In February, 1920, he had influenza, and during the next few months his weakness progressively increased. In the fall of that year he spent four weeks in a sanatorium, and was discharged on a diet that was liberal, including a large quantity of gluten bread. From that time he gradually went down hill, and since February, 1921, he had not been able to work. During the course of the diabetes his weight had fallen from 120 to 85 pounds.

*Physical Examination*—Abnormalities in both pulmonary apices were discovered but no sputum could be obtained.

*Comment*—He was discharged from the hospital June 30, 1921, on a diet which gave him about 30 gm protein, 160 gm fat and 20 gm carbohydrate. He did very well working every day and remaining sugar free until September, 1921, when he developed glycosuria during an extended trip away from home. He returned to the hospital, was sugar free in fourteen days and was discharged on the same diet as previously. He has been able to do his work regularly since that time and is feeling well. Part of his record is presented in Table 9.

It should be noted that five of our 190 patients died in the hospital in coma. Four of these entered the hospital in coma and died without

dietetic treatment In one of these cases, the coma was not accompanied by the usual signs of diabetic coma and at necropsy adenoma of the pituitary gland was found The fifth patient, whose diabetes had been brought under control and who was not showing an acidosis, broke diet and developed a severe acidosis and from this time went progressively down hill, dying in coma None of these deaths can be attributed to the effect of the diet

3 *Nitrogen Balance*—A diet to be satisfactory in the treatment of a chronic disease must be constructed so that it will maintain nitrogen balance In a previous communication<sup>5</sup> it was shown that in the diabetic, as in a normal person, 0.66 gm protein per kilogram of body weight is sufficient for this purpose, provided the total caloric intake is great enough to supply the metabolic needs of the organism By

TABLE 9—SHOWING RELIEF OF MODERATE ACIDOSIS BY HIGH FAT DIET (CASE 8)

Date, 1921	Diet				Urine		CO <sub>2</sub> Combin ing Power Blood Plasma, Vol per Cent	Weight, Lbs
	Protein, Gm	Fat, Gm	Carbohydrate, Gm	Calories	Glucose, Gm	Ferrie Chlorid		
5/19	18.9	80.8	13.9	860	++++	++++	44.7	84.5
5/20	21.7	94.4	14.8	995	20.0	++++		
5/21	20.4	83.3	11.8	875	18.4	++++		85.0
5/22	19.0	95.4	14.2	990	++++	+-++		
5/23	20.9	110.4	15.0	1,125	13.8	++++		
5/24	20.8	89.9	13.4	945	12.3	++++		
5/25	19.4	92.3	14.2	965	10.3	++++		
5/26	21.2	85.9	13.4	910	+++	++++		
5/27	21.9	94.4	14.8	995	++	++++		
5/28	20.8	89.9	13.4	945	Trace	++		88.9
5/29	20.9	85.2	12.4	940	0	++		
5/30	19.1	95.4	14.2	990	0	0		
5/31	15.2	88.2	12.5	905	0	+		
6/ 1	28.0	155.8	21.3	1,660	0	Trace	62.5	90.0
6/ 2	29.7	147.1	20.9	1,525	0	0		

using relatively large quantities of fat, we have been able to satisfy the total caloric requirement of the patient without producing glycosuria and to maintain nitrogen balance on the small quantities of protein that we have allowed The table published in the communication referred to is here reproduced (Table 10)

4 *Lipemia*—A frequent accompaniment of the diabetic state is an increase in the amount of lipid substances in the blood While the true significance of this phenomenon is not known, it is at all events a departure from the normal, and its increase or its persistence during treatment is considered undesirable It has been shown in another communication<sup>6</sup> from this clinic that (1) hyperlipoidemia is not produced by the high fat diet in those patients in whom it is not present

5 Marsh, P. L., Newburgh, L. H., and Holly, L. E. The Nitrogen Requirement for Maintenance in Diabetes Mellitus, *Arch Int Med* 29:97 (Jan) 1922

6 Marsh, P. L., and Waller, H. G. *Arch Int Med* to be published

at entrance, and (2) an existing hyperlipoidemia, even of high degree, gradually falls until it has approximated or reached the normal level. It is, therefore, apparent that a high fat diet does not cause a hyperlipoidemia.

5. *General Condition of the Patient*—Weakness and incapacitation are unavoidable evils resulting from fasting and undernutrition, and the diabetic is not exempt from these ill effects. It was with the hope of avoiding these disadvantages that we undertook an investigation of the use of fat for the purpose of supplying energy to the patient. The desugarization period and the long period of after treatment will be considered separately.

The initial period of fasting is very poorly borne by many of the more debilitated diabetics. When the fasting is continued for a week or more, the resulting exhaustion may be extreme. For example,

TABLE 10—DIETS ON WHICH NITROGEN BALANCE WAS ESTABLISHED IN TWELVE PATIENTS WITH DIABETES MELLITUS

Case No	Age, Years	Weight, Kg	Protein, Gm	Fat, Gm	Carbohydrate, Gm	Calories	Nitrogen, Gm	Protein, per Kg, Gm	Calories per Kg	Per Cent of Total Calories as Carbohydrate
1	56	63	34.3	168.4	6.9	1,680	5.49	0.54	27	16
2	68	66	39.3	221.4	13.8	2,295	6.27	0.59	35	23
3	37	60	54.1	240.1	13.4	2,430	8.66	0.90	41	22
4	18	42	28.5	162.8	9.9	1,615	4.49	0.68	38	24
5	21	50	37.8	163.6	8.2	1,650	6.05	0.75	33	19
6	49	70	65.0	197.0	9.9	2,065	10.04	0.93	30	19
7	22	59	33.5	150.1	25.4	1,585	5.36	0.53	27	64
8	36	69	55.5	207.8	38.7	2,245	8.80	0.79	33	69
9	63	50	31.8	157.4	23.8	1,640	5.09	0.63	33	58
10	80	90	51.4	239.1	33.9	2,265	8.22	0.57	25	60
11	22	55	40.6	200.2	25.0	2,065	6.50	0.74	37	48
12	18	42	30.0	179.6	14.7	1,795	4.80	0.71	43	33

Olmsted,<sup>7</sup> speaking of his experience with the use of fasting in the treatment of diabetes, says "It was soon found that rather severe acidosis followed the period of complete starvation even in relatively mild cases. So impressed were we with the depression and weakness of patients during and following acidosis that some modification of the starvation routine was thought worth trying out." Some of our patients who had previously been subjected to fasting and were later made sugar free by our diet, volunteered the information that the earlier fasting method had left them in a state of exhaustion and extreme weakness and that they were astonished at their strength after they had become sugar free at our hands. The patient who was cited as Case 1, for example, said that after his previous fasting he had no desire to leave his bed, in contrast to this, on his thirteenth day in the hospital, when he became sugar free, he felt fresh after a two mile walk.

<sup>7</sup> Olmsted W. H. M. Clinics N. America 4:865 (Nov.) 1920

Not only is fasting exhausting and unpleasant to the patient, but it may occasionally end in death. The dangers of complete fasting were pointed out in the Rockefeller Monograph<sup>8</sup> on the treatment of diabetes. Case 30 in that series is cited by the authors as "a typical example of acidosis with a fatal result on fasting," and "patient 35 developed malaise, nausea and drowsiness on fasting and the observers were convinced that unless fed he would have died in the typical intoxication." Joslin<sup>9</sup> has reported two patients who died with hypoglycemia as a result of fasting and Wilder<sup>10</sup> has observed that obese diabetics are especially susceptible to severe acidosis from fasting. We have had referred to us a patient who had been fasted for two weeks without becoming sugar free, and who had developed extreme weakness, nausea and vomiting after four days in the hospital, during which she could retain no food, she died quietly without hyperpnea. She retained consciousness up to a minute or two before death. In this elderly

TABLE II—EFFECT OF HIGH FAT DIET ON LIPOIDEMIA

Case No	First Percentage	Last Percentage	Interval, Days	Remarks
21-276	8.1	2.69	66	Case 4, this series
21-321	3.31	1.01	260	Case 1, this series
21-678	2.63	1.00	395	Case 3, this series, complicated by chronic pulmonary tuberculosis
21-1021	1.59	1.34	20	Case 5, this series
21-1002	2.73	1.10	38	Case 6, this series
21-3458	0.802	0.905	40	
21-3456	0.961	0.956	51	
21-3573	1.025	1.009	21	
22-2	1.33	1.15	19	
21-2418	0.869	0.918	14	Previously on diet for four months
22-36	0.930	0.933	17	
22-610	1.126	0.890	33	

patient whose symptoms had not been sufficiently severe during the three years that she had had diabetes to cause her to be treated, fasting ended in disaster. A summary of her record is appended (Case 9). More recently we have had the opportunity of observing a young diabetic in whom a fatal acidosis was precipitated by fasting, a summary of his record will be found as Case 10. The fact that fasting is always unpleasant, often dangerous and sometimes fatal, justifies one in rejecting it in favor of a procedure which avoids these difficulties and at the same time makes the patient sugar free.

CASE 9 (20-709)—*History*—An American housewife, aged 62 years, entered the hospital early in the evening of Nov. 9, 1920, in a state of extreme exhaustion. Little information could be obtained relative to her history. It

8 Allen, F. M., Stillman, E., and Fitz, R. Total Dietary Regulation in the Treatment of Diabetes, Monograph, Rockefeller Institute M. Research, No. 11, 1919.

9 Joslin, E. P. M. Clinics N. America 4 1723 (May) 1921.

10 Wilder, R. M. M. Clinics N. America 5 455 (Sept.) 1921.



was known, however, that she had had diabetes for three years, but that it had never disturbed her enough to cause her to commence systematic treatment. She was persuaded to begin treatment October 15, she was fasted for two days, then given green vegetables for three days, fasted three days more and finally given thrice cooked vegetables until November 5. During the last three days of this diet she became progressively more nauseated and vomited frequently. From November 5 until she entered the hospital she ate little and apparently retained nothing.

*Examination*—At admission she was stuporous, but not unconscious, her speech was thick and she seemed loathe to exert herself sufficiently to talk. There was no hyperpnea, but her breath had an acetone odor. The knee jerks were diminished. Her urine contained albumin, sugar, diacetic acid and hyaline and granular casts. Her blood pressure was 165/70, the carbon dioxide tension of the alveolar air was 30 and blood sugar 0.33 per cent.

*Comment*—During the time she was in the hospital, she retained no food and little of the water that was given her by mouth. Every few minutes, day and night, she vomited. Her temperature was always subnormal. On the night of November 12, she died quietly while the nurse was out of the room for two or three minutes.

CASE 10 (21-3305)—*History*—An American farmer, 26 years of age, entered the hospital Nov 11, 1921, in deep coma. Little history could be obtained but it was stated that diabetic symptoms were first noted less than five weeks before. Polyuria and polydipsia had been present only two weeks. Treatment was started two days before admission with the limitation of his diet to 2 quarts of milk on the first day and then complete starvation. On the morning of the second day of starvation he became stuporous and gradually passed into coma, coming to the hospital that evening.

*Examination*—He was in deep coma with characteristic hyperpnea. His blood sugar was 107 per cent and the carbon dioxide combining power of the blood plasma by the Van Slyke method was 18 volumes per cent. He died about five hours after admission to the hospital. Nothing important was found at necropsy.

We turn now to a consideration of the ability of patients to lead fairly active lives while they adhere to the maintenance diets prescribed for them when they leave the hospital. This diet is so constructed as to avoid the evils of undernutrition. The physiologic effects of undernutrition have been observed on a large scale during the recent war, and a review of these studies has been published by Graham Lusk<sup>11</sup>. These changes in metabolism result in a great mental and physical depression. The undernourished subject not only has not sufficient fuel for normal amounts of work, but lacks the desire to attempt work, mental or physical. Prolonged undernutrition results in chronic invalidism. The patient, if not actually confined to his bed or to a chair, is able to do little more than to get about the house unassisted. The woman who was mentioned above as Case 2 was bed-ridden on a diet allowing her 500 calories a day before she came to us. The condition of such a diabetic is pitiful, even the most moderate activity is denied him and he becomes a burden to his family and to himself.

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<sup>11</sup> Lusk, G. Physiological Effect of Undernutrition, *Physiol Rev* 1 523, 1921.

and an economic loss to society. In contrast to this, our patients have returned to their original occupations, and have a bright, hopeful outlook on life. A few examples are cited.

**CASE 11 (20-19) —History**—A railroad fireman, 22 years of age, entered the clinic Jan 16, 1920, complaining of excessive thirst and polyuria. There was no history of diabetes in the family, and his past history was of no importance. The onset of the disease occurred abruptly during the early part of December, 1919, with polyuria, and increased thirst and appetite. By the first of January he was urinating every hour, and he went to a physician, who diagnosed diabetes. Between January 1 and his admission to the hospital his diet consisted entirely of milk. During the month that he had had diabetes his weight had fallen from 130 to 125 pounds.

**Examination**—Nothing of interest was noted on physical examination. His urine was sugar free on the fourteenth day of a diet containing 16 gm protein, 199 gm fat, 10 gm carbohydrate and 1,000 calories.

**Comment**—January 21, he developed influenza, which was then epidemic, his diet was unchanged and he made an uneventful recovery. Feb 20, 1920, he was discharged from the hospital on a diet containing protein, 25 gm, fat, 175 gm, carbohydrate, 15 gm, 1,800 calories. This was gradually increased to contain protein, 55 gm, fat, 220 gm., carbohydrate, 35 gm, calories, 2,400. Except for the first few weeks after discharge from the hospital he has been working hard and steadily, first in a machine shop and then on his father's farm. On a few occasions he has fired a locomotive and states that he noticed no unusual fatigue. At present, two and a half years after admission, he is working on the farm, says that he feels entirely well and is sugar free on the diet.

**CASE 12 (20-346) —History**—A housewife, 32 years of age, was admitted to the hospital April 19, 1920, complaining of weakness and polyuria. There was no history of diabetes in the family. During her past life she had had many attacks of bronchitis, and she had had one attack of tonsillitis several years before admission. In January, 1919, she had influenza and did not regain her strength after it as she thought she should. She also suffered from polyuria and swelling of the feet. A physician told her that she had diabetes and forbade the use of foods rich in carbohydrate. Her urine had never been sugar free from this time until she came to the hospital, and weakness was progressive. At the time when we first saw her, this latter was her most serious complaint. She stated that she was entirely unable to attend to her household duties or to care for her 6 year old child, and that if she was out of bed for any length of time she fainted and had to be carried back.

**Examination**—Nothing of importance was noted in the physical examination.

**Comment**—On a diet containing 16 gm protein, 95 gm fat, 8 gm carbohydrate and 950 calories her urine became free from sugar on the fourth day and the ferric chlorid reaction was negative on the eighth day. Her diet was increased to contain 55 gm protein, 220 gm fat, 35 gm carbohydrate and 2,400 calories. She has kept in constant touch with us, and with the exception of a short period when she had a severe acute bronchitis, she has always been sugar free, a period of twenty-six months. She is doing her housework, and feels as strong as she did before the onset of her diabetes.

**CASE 13 (19-286) —History**—A Jewish salesman, 40 years of age entered the hospital June 5, 1919, with a diabetes that had developed abruptly ten years before. There was no family history of diabetes, and his previous history was of no importance. At the time of onset of the usual diabetic symptoms, his weight had been 172 pounds, his weight at admission was 136 pounds. His vision had failed rapidly, and when first seen by us his left

eye was almost blind. There had been increasing numbness and tingling of the feet and legs for the past few months, and he was unable to work because of weakness.

*Physical Examination*—This showed nothing of importance, except evidence of peripheral and aortic arteriosclerosis. His blood sugar was 0.40 per cent, his urine contained sugar and diacetic acid and his hemoglobin was 110 per cent with 6,320,000 red blood cells.

*Comment*—On a diet containing protein, 15 gm, fat, 90 gm, carbohydrate, 10 gm, 900 calories, he became sugar free in one day. His diet was increased by steps until he was receiving protein, 48 gm, fat, 243 gm, carbohydrate, 15 gm, calories, 2,440. The patient returned to the hospital March 31, 1920, for examination. His urine was free from sugar and his blood sugar was 0.13 per cent. He had adhered to the diet previously prescribed and was discharged with the same diet. At a third admission, Feb 1, 1921, he was still sugar free, with a blood sugar of 0.12 per cent and no diabetic symptoms. He was discharged on a diet which allowed him protein, 55 gm, fat, 220 gm, carbohydrate, 35 gm, calories, 2,440. In December, 1921, he reported that he is still sugar free and feeling entirely well. During these three years he has been active as a traveling salesman, and has in no way been disturbed by his diabetes. His weight is 120 pounds.

CASE 14 (18-519)—*History*—An American farmer, 57 years old, entered the hospital Oct 10, 1918, complaining of weakness and ulcer on his foot. He had always been healthy until eight years before when he began passing large quantities of urine. Aside from the omission of bread from his diet, there had been no treatment of the diabetes. On two previous occasions he had ulcers on his feet that were slow in healing. The one that brought him to the hospital appeared about five weeks before. Eight years before he weighed 187 pounds and his admission weight was 129 pounds.

*Examination*—Arteriosclerosis was marked, his urine contained diacetic acid and 63 gm glucose in the first twenty-four hour specimen, and his blood sugar was 0.59 per cent.

*Comment*—October 24, his urine was free from sugar and his diet was increased by steps until it contained 3,050 calories, from 60 gm protein, fat, 300 gm, and carbohydrate, 25 gm. He was left on this diet until Oct 21, 1921, when it was changed to contain protein, 55 gm, fat, 220 gm, carbohydrate, 35 gm, and 2,340 calories. The patient's wife, who has been caring for his diet, says that he has adhered to it religiously, and that during the whole time he has been able to do his work on the farm.

6 *Prognosis*—The question naturally arises as to whether or not all these advantages accrue to the diabetic at the expense of duration of life. That is, will the use of a diet such as we have advocated cause in itself a downward progress of the disease with a loss of tolerance and an earlier death than might be expected under the other methods of treatment. While our experience with high fat diets is still brief in proportion to the chronicity of the disease and we must therefore be somewhat cautious in our conclusions in this regard, we have as yet seen no reason for believing that such is the case. We have a certain amount of information that seems to bear on the question and which apparently indicates that the prognosis in patients on the high fat, low protein diets is at least as good as that in patients on other diets.

Such evidence may be obtained in both of two ways, first, by recording any change in tolerance that may occur in individual cases

from time to time during the prolonged use of the diet, second, by a statistical comparison of the outcome in our patients with that of patients on other diets

*Carbohydrate Tolerance*—While we have not as yet observed a sufficient number of patients over a sufficient length of time to make us willing to affirm that this treatment is never attended by downward progress, we have been able to follow some severe cases of diabetes long enough to show that a diet containing roughly the normal caloric requirement is at least not inevitably attended by loss of tolerance within the period of observation. The records of several such patients have been presented in summary in this paper.

In our whole series we have seen no evidence of loss of tolerance in a patient who has adhered to the diet and, therefore, we have no reason for believing that downward progress is an accompaniment of a maintenance diet. We had one patient under observation in whom diabetes was complicated by a wide spread pulmonary tuberculosis whose capacity for the utilization of carbohydrate steadily declined until he died of the tuberculosis fourteen months after the initiation of treatment. A similar loss of tolerance from a pyogenic infection was observed in Case 15. The disastrous effect of infections on the glucose tolerance of diabetics is well known, and in these cases explains the observed downward progress.

CASE 15 (21-3332)—*History*—A boy, aged 7, came for treatment Nov 14, 1921, with diabetes that had developed in connection with a suppurative mastoiditis in May, 1920. He had had careful dietetic treatment during the interval and for several months previous his diet had contained protein, 60 gm, fat, 60 gm, and carbohydrate, 10 gm, on which he had had glycosuria most of the time. He was desugarized by a diet containing protein, 25 gm, fat, 100 gm, and carbohydrate, 12 gm. His diet was increased to protein, 30 gm, fat, 130 gm, carbohydrate, 18 gm.

During January, 1922, he developed an acute upper respiratory infection and eventually a pansinusitis. Glycosuria returned in a progressively increasing degree and he died May 20, 1922.

*Duration of Life*—Conclusions regarding the duration of life in relation to any treatment used in the management of a chronic disease are difficult to draw because of the many more or less unavoidable sources of error that enter into a biologic problem of this sort. Statistical compilations of the average duration of life in years of diabetics undergoing different forms of treatment might at first thought seem to answer the question mathematically and beyond doubt. But statistics to be of value must deal with only one variable or else all other variables must be thoroughly understood and be under control. Such is not the case in the present problem. Some of the improperly controlled variables which inevitably occur in series of cases extending over long periods of time are the following

1 The term diabetes mellitus is applied to several types of persistent glycosuria which vary greatly in severity and prognosis regardless of treatment Wilder<sup>10</sup> recently made another effort to classify diabetics, and divided them into five groups whose clinical manifestations and progress are so different as to make them seem like different diseases Unless series that are being compared contain equal percentages of the different kinds of diabetics, deductions from the statistics will be erroneous in just so far as the types represented are numerically unequal

2 It is probably true that all diabetics are guilty at one time or another of small indiscretions in diet, and many of larger ones The effect of such indiscretions on duration of life is not known and therefore becomes a variable whose magnitude is undetermined Experience seems to show that the effect of indiscretion varies enormously from patient to patient For example, the patient reported as Case 16 died apparently as the result of a single indiscretion, while the patient reported as Case 17 appears to have recovered from her diabetes while living on an unrestricted diet

**CASE 16 (19-170) —History**—A woman, 38 years of age, entered the hospital April 3, 1919, because of sexual anesthesia and diabetes She stated that her nine children had diabetes, but this could not be verified Her diabetic history was not clear cut, consisting of pruritis vulvae at intervals since the age of 14, nocturia as long as she can remember, tingling of her legs for fifteen years, boils nine years before and glycosuria first discovered in 1910 Her weight at the age of 21 was 135 pounds, and at admission to the hospital was 131 pounds

**Examination**—Her blood sugar at admission was 0.57 per cent and her urine contained 74 gm glucose in the twenty-four hour specimen

**Comment**—On a diet containing 16 gm protein, 90 gm fat and 10 gm carbohydrate her urine became sugar free on April 17, and her blood sugar was 0.19 per cent At this time her husband brought her some food beyond what had been prescribed, glycosuria returned, her blood sugar rose to 0.32 per cent, vomiting developed, and her general condition became progressively worse Actual coma did not appear until May 3 after three days of fasting and she died the next day

**Pathologic Diagnosis from Necropsy**—Diabetic coma, subacute parenchymatous nephritis, acute toxic hepatitis, thyroid adenoma, atrophy and fibrosis of pancreas

**CASE 17 (19-38) —History**—A girl, aged 18, was transferred to our clinic from the department of genito-urinary surgery, Jan 22, 1919 She had come to the hospital for treatment of gonorrhea, and glycosuria had been discovered during the routine urine examination There had been no diabetic symptoms Her father and mother had died during her childhood and no family history could be obtained

**Examination**—Her general examination showed nothing of importance The urine contained 184 gm glucose in the first twenty-four hours, but she insisted on leaving the hospital

**Comment**—A letter from her home physician states that her urine is sugar free and that she is feeling entirely well without dieting

3 The prognosis in diabetes is very closely related to the complications of the disease. Diabetics treated in institutions of different types show variations in percentages of individual complications. The clinic situated in a region to which many patients come from long distances for the treatment of tuberculosis sees more diabetic patients with tuberculosis than does the average clinic. In a hospital known chiefly for its surgery, the internist cares for a large percentage of diabetics with surgical diseases. The diabetic specialist in a large general hospital must add to his group many patients entering because of serious infections and major surgical conditions, to whom the diabetes is unknown or of minor importance, whereas the physician confining himself to the treatment of private diabetic patients is less likely to have to care for these milder cases of diabetes in which life is ended by the major diseases which brought the patients to the hospital. The statistical outcome of a group is importantly affected by the number of patients who enter the hospital in coma, but this number will vary with the location of the hospital. The general hospital in the big city will receive more such cases than an institution such as the university hospital located as it is in the small town, since patients in coma are not transported a long distance to a hospital.

4 Diabetics are subject to the prevalent small infections. The lasting effect of these small infections cannot be guessed at. Furthermore, statistics concerning any group of diabetics may be seriously affected by an epidemic in their community, for example, three of the seventy-three patients originally reported on by us died of influenza. While influenza was pandemic in this country at the time, it illustrates the fact that such a disease may influence the statistics either because of its effect on a small series of cases, or because it might be local.

5 It is obvious that statistics dealing with the duration of life from the onset of the diabetes are greatly influenced by the efficacy of the treatment before the patient came to the physician compiling the statistics. The previous treatment may effect the total duration of the disease in either of two ways, either the proper management of the patient may have given him a long life before he came to the physician reporting the statistics, or improper treatment may have aggravated the disease or allowed complications to develop that injure the prognosis. For example, the appearance of our statistics on young diabetics is improved by the addition of Case 1, the patient having been kept alive for seven years by previous treatment, while the patient described as Case 18 (cited below) was mildly diabetic, and came to us with an overwhelming and fatal infection which had been allowed to develop because her diabetes was uncontrolled.

CASE 18 (21-1507) —*History*—A housewife, 57 years of age, entered the hospital June 2, 1921, with a massive infection in her feet and legs, complaining of the usual symptoms of diabetes. Six years before she was troubled by pruritis vulvae, and during the following year polyuria and polyphagia developed. At this time a physician diagnosed the diabetes. For eight weeks she was on a diet of green vegetables and bran, but since that time there had been no dietetic treatment. Her weight fell from 200 pounds to 140 pounds. Her vision had been failing for a year and constipation had been obstinate. About four years ago she began having blisters on her feet which would rupture, heal very slowly and then appear again. Several weeks ago her feet became swollen, red, and so painful that she could not walk on them.

*Examination*—On examination it was noted that there was marked sclerosis of the peripheral vessels and evidence of aortic sclerosis. The knee jerks four years ago she began having blisters on her feet, which would rupture, heal very slowly and then appear again. Several weeks ago her feet became swollen, red, and so painful that she could not walk on them.

*Comment*—Throughout her stay in the ward she had an irregular fever and a leukocytosis of from 22,300 to 35,300. Her hemoglobin was 60 per cent and she had 3,050,000 red cells. Her blood sugar was 0.21 per cent and her urine contained sugar but no diacetic acid. In spite of free drainage of her feet, chills and fever continued, she became weaker, the pulse feebler, respirations slower and she died during the night of June 12.

6 Accurate knowledge of the length of life after the onset of diabetes is often unobtainable because of the impossibility of determining the date of onset. The discovery of glycosuria by the insurance examiner or during the routine urinalysis in a hospital gives one no information about the duration of the disease up to that time. Some patients cannot remember when the symptoms began, others mention symptoms many years before which may or may not have been diabetic, and in others the onset was so insidious that the physician cannot determine the date of onset.

7 The statistical outcome of the treatment of a group of patients must be influenced by the type of subjects with whom one has to deal. The prognosis is influenced by the patient's intelligence and his social status. It is probable that the improvement during the last decade in the treatment of diabetes has been due very largely to the realization of the importance of instructing the patient in his own care. This instruction can be carried only as far as the patient has ability to learn. It follows then that the prognosis in a given case is largely dependent on the subject's mental capacity. One of our patients is suffering from Korsakoff's psychosis and entirely unable to care for herself, another, with a condition diagnosed constitutional psychopathic state by the department of psychiatry, whose family is trying to keep him to the diet, is reported to be stealing food from the garbage cans of the neighborhood. The deaths of such patients from diabetes or any other cause bear no relation to attempts at treatment.

The social status of the patient influences the prognosis because of two factors. Persons compelled to obtain their food at public eating

houses find it impossible to adhere rigidly to the diet because of inability to obtain proper foods or to have them measured. One of our patients, a farm hand, is very much discouraged because he has not been able to find work on a farm where his diabetic meals will be prepared for him. Others, under economic pressure, are unable to increase their expenses by the small amount necessary to supply the diet. One of them is living on thirty cents a day, and eats little but rolls and coffee.

8 An important variable in the statistical study of diabetics is the physician himself. Success in the treatment depends, in part, on the ability of the physician in impressing on the patient the importance of adhering to the diet, and, in part, on the amount of instruction that can be given the patient in the management of his food. In the comparison of statistics from different institutions these elements cannot be ignored.

9 An important factor in the success of treatment of diabetes is the home physician. The adherence of the patient to a diet depends, in part, on the belief of the home physician in the importance of strict adherence. The damaging effect to statistics of lack of cooperation between the specialist and the general practitioner is shown in the following example (No 19).

CASE 19 (20-475) —*History*—An American woman, aged 33 years, entered the hospital July 12, 1920, complaining of weakness and loss of weight. There was no family history of diabetes. Her diabetes developed abruptly in July, 1919, with polyphagia, polydipsia, polyuria, weakness, and loss of weight. For the past six months she had noticed progressively increasing numbness of her arms and legs. Her weight at the onset of the disease was 109 pounds and her weight at admission was 61 pounds.

*Examination*—Except for loss of the knee and Achilles reflexes, her physical examination was negative. Her blood sugar was 0.42 per cent, and her urine gave a strong reaction to ferric chlorid.

*Comment*—On the tenth day of a diet containing 15 gm protein, 90 gm fat, and 12 gm carbohydrate, her urine gave a negative reaction to ferric chlorid and was sugar free. She was discharged from the hospital August 28 without glycosuria or evidence of acidosis on a diet which allowed her 28 gm protein, 140 gm fat and 20 gm carbohydrate. A letter from her sister stated that she adhered to the diet until late in October when the family physician advised her to let the patient have anything she wanted. She died Nov 18, 1920.

We have cited a number of important reasons for using great caution in applying statistics to the study of the comparative effects of different treatments on the course of the disease in the diabetic patient, but in spite of these objections there is undoubtedly something to be learned from the tabulation of the available data concerning the status of our 190 patients. This information is contained in Table 12.



It will be noted that of these 190 patients, treated between March 1, 1918, and July 1, 1922—a period of four and one third years—forty-five (23.7 per cent) are dead, fourteen (7.4 per cent) are not traced and 132 (68.9 per cent) are alive. If the fifteen patients who died in

TABLE 12 — PRESENT STATUS, BY DECADE OF ONSET AND YEAR OF FIRST TREATMENT, OF ALL PATIENTS TREATED SINCE INCEPTION OF HIGH FAT DIET

	Age of Onset								Total
	0-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	
Total Cases									
1918	0	0	5	4	2	5	1	0	17
1919	1	4	3	6	10	10	3	1	38
1920	1	0	6	5	7	13	2	0	34
1921	3	7	8	10	7	18	11	1	65
1922	1	3	2	8	11	10	0	1	36
Total	6	14	24	33	37	56	17	3	190
Died in Hospital									
1918			2						2
1919		1		1		1			3
1920				1	2	1	1		5
1921			1			1			2
1922			1		1	1			3
Total	0	1	4	2	3	4	1	0	15
Dead—Discharged Untreated									
1918				1					1
1919					1	1			2
1920			2						2
1921		1							1
1922									0
Total	0	1	2	1	1	1	0	0	6
Died—Treated									
1918			1			2			3
1919		2				1			3
1920			2	2	3	3	1		11
1921	1		2			1	1	1	6
1922						1			1
Total	1	2	5	2	3	8	2	1	24
Untraced									
1918				1		1	1		3
1919			2	3	1	1	1		8
1920				1		1			2
1921							1		1
1922									0
Total	0	0	2	5	1	3	3	0	14
Alive									
1918			2	2	2	2			8
1919	1	1	1	2	7	5	2	1	20
1920	1		2	1	3	9			16
1921	2	6	5	10	7	16	9		55
1922	1	3	1	8	10	8		1	32
Total	5	10	11	23	29	40	11	2	131
Summary									
Total cases									190
Total dead									45
Total missing									14
Total alive									131

the hospital, the eight who were discharged against advice with glycosuria and the fourteen who are untraced be subtracted from the total of 190, there remain 153 who were discharged sugar free. These 153 patients are the only ones who give us evidence concerning the effect of

the diet when used over a long period of time. Of these 153 patients, twenty-four (15.7 per cent) are dead and 129 (84.3 per cent) are living. Obviously, there is no way of knowing how many of these patients adhered rigidly to the prescribed diets.

The forty-five dead patients fall into three groups: viz, fifteen who died in the hospital, six who were discharged against advice with glycosuria and twenty-four who died after having been discharged from the hospital sugar free. The first group is presented in Table 13. It will be seen that five of these died in coma, of these four entered in coma and were not treated by the method under discussion, the fifth went into coma after breaking diet. The patient who died

TABLE 13—PATIENTS DYING IN HOSPITAL

Number	Date of Admission	Date of Death	Condition at Admission	Cause of Death	Age at Onset	Age at Death	Remarks
18-639*	11/11/18	11/12/18	Coma	Coma		29	No history
18-679	12/ 8/18	9/30/20		Chronic pulmonary tuberculosis	26	28	No glycosuria, no acidosis at death
19-170	4/ 3/19	5/ 4/19		Known to have broken diet, coma	?	38	
19-641	1/29/20	1/30/20	Influenza	Pneumonia	33	36	
19-650	12/26/19	12/29/19	Coma	Coma	57	60	
20-423	6/ 7/20	7/13/20	Hematuria	Broncho pneumonia	61	63	No glycosuria nor acidosis at death
20-443	6/16/20	6/28/20	Advanced tuberculosis	Pulmonary tuberculosis	45	46	No glycosuria nor acidosis at death
20-481	7/14/20	7/15/20	Suppurative mastoid, coma	Septicemia	35	47	
20-709*	11/12/20	11/12/20	Exhaustion vomiting	Inanition	59	62	Previous fasting
20-753	12/ 3/20	12/17/20	Ventral hernia	Postoperative pneumonia	46	48	Died in surgical ward, necropsy, mild diabetes
21-1507*	6/ 2/21	6/13/21	Osteomyelitis of foot	Septicemia	53	59	
21-3305	11/11/21	11/11/21	Coma	Coma	26	26	
22-27	1/10/22	2/ 2/22	Pyelonephritis, pyemia	Septicemia	49	50	No glycosuria nor acidosis at death
22-399	2/13/22	2/15/22	Coma	Coma	24	27	
22-477	3/16/22	4/15/22	Gangrene legs	Gas gangrene	53	56	Necropsy

\* Summary of record elsewhere in paper

of inanition as the result of previous fasting has been described as Case 9. All but two of the remaining cases died of infection acquired before entering the clinic. One patient (20-753), mildly diabetic, died of pneumonia following an operation for repair of a ventral hernia at a time when she was sugar and ketone body free. The remaining patient (20-423) died of bronchopneumonia following cystoscopy, without glycosuria or evidence of acidosis. None of these deaths are of significance in estimating the value of the high fat diet.

The status of the patients who left the hospital against advice is presented in Table 14. Seventy-five per cent of the patients who refused dietary treatment are dead. This emphasizes again the importance of keeping the diabetic sugar-free regardless of the method employed.

The twenty-four patients who died after leaving the hospital on the diet are presented in Table 15. Four patients are known to have died in coma and all of them are known to have discarded the diet.

TABLE 14—STATUS OF PATIENTS LEAVING HOSPITAL AGAINST ADVICE WITH GLYCOSURIA

Case No	Date of Admission	Date of Discharge	Date of Onset	Date of Death	Age at Onset	Age at Admission	Age at Death	Duration After Discharge	Cause of Death or Condition if Alive
18-263	5/27/18	6/4/18	Jan., 1918	7/1/18	35	38	38	1 month	?
18-468	9/12/18	9/16/18	Jan., 1918		39	39			Refused treatment, glycosuria
19-33	1/22/19	2/14/19	?		?	18			Unrestricted diet, no glycosuria
19-411	8/26/19	9/3/19	1917	12/14/20	51	53	54	12 years	"Chronic diarrhea"
19-201	4/17/19	4/26/19	1914	July, 1921	47	52	54	22 years	Gangrene both legs
20-516	8/5/20	8/12/20	1915	8/20/20	30	35	35	1 week	Coma
20-676	10/21/20	10/27/20	March, 1920	9/29/21	26	26	27	12 years	Coma
21-3115	10/31/21	11/1/21	June, 1921	Jan., 1921	15	15	16	8 months	Pneumonia

TABLE 15—CASES DISCHARGED WITHOUT GLYCOSURIA

No	Date of Admission	Date of Death	Age at Onset	Age at Death	Cause of Death	Total Duration, Years	Duration After Start of Treatment	Remarks
18-168	4/10/18	10/1/21	57	66	Diabetic gangrene	8.5	3½ yrs	Chronic nephritis with hypertension
18-298	6/12/18	Spring, 1921	53	59	Apoplexy	6.0	2 yrs	
18-382	7/23/18	Jan., 1919	27	31	Influenza	4.0	6 mos	
19-218	4/28/19	1/7/20	58	60	Uremia	11.0	14 mos	Mild diabetes, severe nephritis
19-229	5/1/19	5/9/19	50	55	Carcinoma of uterus	5.0	1 yr	
19-263	5/22/19	11/23/19	61	67	?	6.0	6 mos	
19-306	6/20/19	1/21/22	64	70	Gangrene	6.0	2.6 yrs	
19-444	9/5/19	2/8/19	16	18	Influenza	2.0	6 mos	
19-537	10/22/19	July, 1920	20	21	Coma	1.5	9 mos	Motor trip ate everything, died short time after arriving
20-24	1/20/20	Aug. 1920	26	27	?	1.0	8 mos	
20-211	2/19/20	4/18/21	50	59	Apoplexy, Bright's disease	8.8	14 mos	Mild diabetes, severe nephritis
20-294	3/23/20	5/24/20	27	28	Convulsions	0.8	2 mos	Cerebrospinal syphilis
20-426	6/8/20	Sept., 1920	33	34	Coma?	1.4	3 mos	
20-427	6/9/20	May, 1922	44	47	?	3.2	23 mos	
20-475	7/12/20	11/18/20	32	33	Coma	1.2	4 mos	Home physician told her to eat what she wanted, died two weeks later
20-486	7/16/20	2/1/22	62	68	Cardiac failure	5.7	1.5 yrs	Chronic myocarditis
20-632	10/1/20	7/5/21	59	65	Carcinoma of breast	6.0	8 mos	
21-19	1/10/21	2/15/21	71	76	Apoplexy	5.2	1 mo	Mild diabetes, severe nephritis
21-276	2/7/21	Jan., 1922	21	22	Coma	1.3	11 mos	Tried "patent medicine", died in three weeks
21-2329	8/17/21	1/22/22	54	64	Chronic pulmonary tuberculosis	10.3	5 mos	Advanced tuberculosis at admission
21-2703	9/20/21	3/5/22	52	53	Coma	1.3	5 mos	Left against advice
21-2954	10/12/21	Feb., 1922	61	68	Angina pectoris	7.4	4 mos	
21-3332	11/14/21	5/12/22	6	8	Maxillary sinusitis	2.0	6 mos	
22-1246	5/3/22	6/2/22	55	55	?	0.3	1 mo	Discharged against advice, sugar free

A fifth is believed to have died in coma, though little is known about her death. That is, of 167 patients discharged sugar free, only five have died in coma, and four of these are known to have discarded their diet. These statistics demonstrate clearly the innocuousness of the

high fat diet in relation to the induction of acidosis. Two died of gangrene. The rest died of causes not primarily diabetic.

A summary of the causes of death of all these forty-five patients, including those who died in and out of the hospital, is found in Table 16. Joslin<sup>12</sup> has pointed out that coma as a cause of death has decreased from 68 per cent of his fatal cases treated before 1914 to 55 per cent since he has employed fasting and severe undernutrition. This he cites as evidence of improvement in treatment. It is, therefore, interesting to note that in our relatively small series of fatal cases, only 27 per cent have died in coma.

TABLE 16—CAUSES OF DEATH IN ALL KNOWN TO HAVE DIED SINCE THE INCEPTION OF HIGH FAT DIET

	Number	Per Cent		Number	Per Cent
Coma	12	26.7	Uremia	1	2.2
Gangrene	4	8.6	Central nervous system		
Pneumonia	6	13.3	syphilis	1	2.2
Tuberculosis	3	6.7	"Chronic diarrhea"	1	2.2
Septicemia	3	6.7	Carcinoma	2	4.4
Intoxication	1	2.2	Apoplexy	3	6.7
Angina pectoris	1	2.2	Suppurative sinusitis	1	2.2
Cardiac failure	1	2.2	Unknown	5	11.1

TABLE 17—STATUS OF ALL PATIENTS AFTER MORE THAN FOUR YEARS USE OF TREATMENT

	Williams		Authors' Series	
	Number	Per Cent	Number	Per Cent
Total	304	100	176*	100
Living	201	66	131	75
Dead	103	34	45	25

\* Excluding 14 cases lost

While we have pointed out the pitfalls encountered in the use of comparative statistics, it may, nevertheless, be of some value to tabulate our results beside those of competent observers using other methods. It is, of course, not necessary to compare this group with one treated previous to 1914 because of the great improvement in the treatment of diabetes mellitus that followed this date. Comparison, however, with such statistics as those of Williams<sup>13</sup> dealing with 304 cases treated during the five year period 1915-1920 may be profitable (Table 17).

Allen<sup>14</sup> has recently published the end results in patients treated in the Physiatrie Institute during 1919, 1920 and 1921. Since 'the

12 Joslin, E. P. Today's Problem in Diabetes Mellitus in Light of 930 Fatal Cases, *J. A. M. A.* **78** 1506 (May 20) 1922

13 Williams, J. R. Evaluation of the Allen Method of Treatment of Diabetes Mellitus, *Am. J. M. Sc.* **162** 62 1921

14 Allen, F. M., and Sherrill, I. W. Clinical Observations on Treatment and Progress in Diabetes, *J. Metabolic Research* **1** 391, 1922

number of patients lost from observation is not tabulated, a strict comparison may not be warranted. In Table 18 the percentage of deaths of the two groups treated is presented, all deaths are included for each observer, regardless of the condition of the patients at admission or their adherence to treatment.

Allen has further tabulated his mortality by excluding those patients who came to him with gangrene, tuberculosis, serious acidosis and neoplasms and subsequently died of such complications. In Table 19 we have compared our mortality with Allen's on this same basis.

A third comparison may be made with the mortality statistics recently published by Joslin<sup>12</sup> of the group treated by him, in hospitals, during the period between April 1, 1919, and December 31, 1922. In Table 20 will be found his data and those of the corresponding group of our series. It will be noted that 8 per cent of our patients

TABLE 18—COMPARISON OF ALLEN'S AND AUTHORS' STATISTICS  
FOR 1919, 1920 AND 1921 AS OF JAN 1, 1922

	Total	Dead	Mortality, Per Cent
Allen	504	86	17.1
Authors' series	137	26	18.8

TABLE 19—SIMILAR COMPARISON WITH DEATHS OF PATIENTS ENTERING WITH  
GANGRENE, TUBERCULOSIS, SERIOUS ACIDOSIS AND NEOPLASM OMITTED

	Total	Dead	Mortality, Per Cent
Allen	480	62	13.0
Authors' series	128	17	13.3

died in the hospital, whereas only 2 per cent of Joslin's died in the hospitals. Since our greater initial mortality is not related to the dietetic plan, it does indicate that we receive a considerably larger proportion of patients who are suffering, when first seen, from serious illnesses which will shortly end their lives, regardless of their diabetic state. In spite of this our mortality is slightly less than his. It is also worthy of note that the average duration of life of those dying in his series was 4.5 years, and in ours, 4.8 years.

It is apparent that, in so far as our statistics go and in so far as deductions from them are justifiable, there is no shortening of the duration of life of the diabetic by the use of a low protein, low carbohydrate, high fat, maintenance regimen. The advantage to the diabetic patient of a diet deriving most of its energy from fat, which, while still controlling the diabetic state, allows him a wide range of activities and avoids the chronic invalidism of severe undernutrition, is apparent. This is admitted by the most ardent adherents of the

undernutrition regimen, provided it can be demonstrated to them that such a diet does not increase the danger of coma nor shorten the duration of life. We have shown that these two fears are groundless. None of our patients has gone into coma as the result of the initiation of this treatment and only half as large a percentage of our fatal cases have resulted in death in coma as in Joslin's series. Our mortality statistics are not importantly different from those of the observers who use severe undernutrition. The improvement in the treatment of diabetes since the introduction of undernutrition in 1914 is undoubted. The high fat maintenance regimen has been shown to permit the diabetic the same expectancy of life as undernutrition. Since the high fat regime carries the out-standing benefit of undernutrition, namely, an increased duration of life, and at the same time avoids the incapacity that inevitably results from prolonged undernutrition, it must necessarily follow that undernutrition should be supplanted by this dietetic method.

TABLE 20—DIABETIC PATIENTS TREATED FROM APRIL 1, 1919, TO DEC 31, 1922, ON JAN 1, 1922

	Authors		Joslin <sup>15</sup>	
	Number	Per Cent	Number	Per Cent
Cases, total	124	100	536	100
Cases, traced	117	94	508	95
Deaths in hospital	10	8	11	2
Deaths in and outside hospital	26	21	118	23

*7 Minor Considerations*—Besides these six major considerations which must enter into a discussion of the treatment of diabetes, there are a few matters of less importance which, nevertheless, should not be ignored in judging of the value of any dietetic regimen. Chief among these are palatability of the diet, its safety in relation to surgical operations and its effect on the gastro-intestinal tract.

On first thought it would seem that it must be difficult to provide diets containing so much fat and so little carbohydrate that are still palatable. To the skilled dietitian this is not a serious problem. Not only can the meals be made attractive, but sufficient variety can be offered so that there is no monotony and the patient need not be surfeited with any one kind of food <sup>15</sup>

The surgeon will ask whether such a diet as has been described may properly be used as a preparation for operation. We have had a not inconsiderable experience in this matter, and we have not varied from our routine in preparing our patients for operations. Such minor operative procedures as tooth extractions, tonsillectomies, and

<sup>15</sup> Stewart, D. Feeding High Fat Diets in Diabetes, *Mod Hosp* **18** 164, 1922

extraction of cataract have been frequent. Several have had amputations of fingers or toes, removal of osteomyelitic bones, and uterine curettages. We have had to deal with the usual number of diabetics who required major surgical operations. None of these patients has developed a serious acidosis. One patient died of postoperative pneumonia which complicated the repair of a ventral hernia without the reappearance of glycosuria, at necropsy a wide spread pneumonia of the influenzal type was found. The remainder of the patients made an uneventful convalescence.

It might be questioned whether a diet so rich in fat may not be accompanied by diarrhea. Such has not been our experience, in no one of our 190 cases has our diet been responsible for a diarrhea.

#### SUMMARY OF RESULTS

A low protein, low carbohydrate, high fat diet fed a large group of diabetic patients since March 1, 1918, (1) produced and maintained an aglycosuric state, (2) was not attended by acidosis and caused its disappearance when present (short of coma) at the beginning of treatment, (3) maintained nitrogen balance, (4) did not cause a hyperlipoidemia and was attended by its disappearance in those patients in whom it was present at entrance, (5) supplied sufficient energy to (a) avoid the evils of fasting and undernutrition and (b) permit an amount of activity compatible with earning a livelihood, (6) was, within the limits of our observations, not attended by downward progress in uncomplicated cases.

#### DISCUSSION

In the construction of the diet that we have recommended we had in mind as the first requirement that its glucose equivalent be low in relation to the total calories. Since all of the carbohydrate, 58 per cent of the protein, and, perhaps, 10 per cent of the fat, are converted during metabolism into glucose, it is apparent that such a diet must be composed chiefly of fat. If the glucose equivalent of different types of diabetic diets are calculated by means of these figures, as suggested by Woodyatt<sup>10</sup> the interesting results shown in Table 21 are obtained.

It is apparent that the high fat diet throws into the metabolism much less glucose in proportion to its caloric content than do the other two types of diet.

*Relation of High Fat Diets to Acidosis*—Owing to the lowered capacity of the diabetic to burn glucose, there is a proportional decrease in his ability to burn fat. Some glucose must be oxidized to assure the complete oxidation of fat. The maximum fat-carbohydrate ratio

that is safe has not been established beyond question. On the basis of the available data, Woodyatt<sup>16</sup> has suggested that if the ratio  $\frac{\text{Fatty Acid}}{\text{Glucose}}$ <sup>17</sup> is greater than 1.5, acidosis will develop. Our standard

diets far exceed this ratio. For example, a standard maintenance diet, composed of protein, 55 gm, fat, 220 gm, carbohydrate, 35 gm, gives a ratio of 2.5. In spite of these high fat values none of the patients developed an acidosis. Of still more importance is the fact that in those patients who came in with an acidosis short of coma, this acidosis has disappeared on the diet. Furthermore, we have even exceeded such high fat-carbohydrate ratios in individual cases without the induction of acidosis. A striking example of this was presented as Case 2. Reference to Table 3 will show that this young diabetic, who entered the hospital with a marked acidosis as shown by his clinical condition, the carbon dioxide combining power of his blood plasma and the ferric chloride reaction of his urine, showed a prompt

TABLE 21—GLUCOSE EQUIVALENTS OF DIFFERENT DIETS

Protein	Fat	Carbohydrate	Calories	Glucose Equivalent
180	138	10	2,000	128.4
90	113	130	2,000	193.6
30	187	30	2,000	78.1

disappearance of the symptoms and signs of the acidosis on our routine desugarization diet. Later he tolerated without acidosis a maintenance diet whose  $\frac{\text{Fatty Acid}}{\text{Glucose}}$  was 4.1. Our experience with

this group of diabetics has convinced us that much higher fat-carbohydrate ratios than those allowed by the calculation of Woodyatt may safely be employed.

Ladd and Palmer<sup>18</sup> have also studied the question of the carbohydrate-fat ratios in relation to ketonuria. Diabetic patients were freed from sugar, their sugar tolerance determined and they were then placed on diets which contained enough protein to maintain nitrogen equilibrium with the fat and carbohydrate given. During different periods the protein was kept constant and the amount of carbohydrate was reduced in proportion to the fat until ketone bodies showed a definite increase in the urine. Table 22 shows the percentage relationship of fat and carbohydrate and the total available carbohydrate

16 Woodyatt, R. I. Objects and Method of Diet Adjustment in Diabetes Mellitus, *Arch. Int. Med.* **28** 125 (July) 1921.

17 Fatty acid = 0.9 fat plus 0.46 protein, glucose = carbohydrate plus 0.58 protein plus 0.1 fat.

18 Ladd, W. S., and Palmer, W. W. The Carbohydrate-Fat Ratio in Relation to the Production of Ketone Bodies in Diabetes Mellitus, *Proc. Soc. Exper. Biol. & Med.* **18** 109, 1921.



(calculated by adding 58 per cent of the protein to the carbohydrate) in the diet of the patients at the point where the ketone body excretion showed a marked increase. In one of our standard diets containing 35 gm protein, 160 gm fat and 20 gm carbohydrate, the corresponding ratio is 1 4

Shaffer<sup>19</sup> who has been studying the relation of the distribution of the foodstuffs burned in different metabolic states to ketosis, has insisted on the importance of the total metabolism in this relation. An outcome of his work is the development of a formula by means of which one may derive the amount of carbohydrate that must be given in the maintenance diet of an aglycosuric diabetic to prevent ketosis. The formula is as follows:

$$\frac{\text{Total Calories} - (100 \times \text{Urine N})}{50} = \text{C H in food}$$

If this formula is applied to our diets, it will be seen that a maintenance diet containing 55 gm protein, 220 gm fat and about 2400 calories should include 31 gm carbohydrate to prevent ketosis. Our

TABLE 22—CARBOHYDRATE-FAT RATIO WHEN KETONURIA APPEARED  
(LADD AND PALMER)

Case No	Gm Available Carbohydrate	Gm Fat	Ratio
101	60 0	150 6	1 2 5
102	25 1	111 0	1 4 4
103	40 9	80 4	1 1 9
104	31 4	140 1	1 4 5
105	25 4	80 5	1 3 2
106	25 6	80 1	1 3 2
107	51 6	235 3	1 4 6
109	28 0	129 9	1 4 0
110	36 6	84 1	1 2 3

diet containing these amounts of protein and fat does in fact contain 35 gm carbohydrate. In a similar manner, a patient weighing less may be maintained in nitrogen and caloric balance on a diet containing 35 gm protein, 165 gm fat, 25 gm carbohydrate, 1725 calories, the combustion without ketosis of these amounts of protein and fat would, according to Shaffer's formula, require 23 gm carbohydrate. Shaffer's fundamental analysis of the mechanism of acidosis, fully justifies the use in practice of these high fat diets.

The important conclusion to be derived from our experience with these 190 cases is that the fear of the use of fat in the treatment of diabetes mellitus is exaggerated, and that fat may be used, as we have used it, without danger of acidosis. On the other hand, we do not want to insist on the employment of the exact proportions of the foodstuffs that we have used. It is possible that other combinations may

19 Shaffer, P. A. The Ketogenic-Antiketogenic Balance in Man, and Its Significance in Diabetes, *J Biol Chem* 50 (Proc) XXVI, 1922

have their advantages in individual cases. The essential fact is that diabetics can tolerate without acidosis low protein maintenance diets containing four times as much fat as carbohydrate.

*Advantages of Limitation of Protein.*—In the dietetic treatment of any disease over a long period of time it is of prime importance that nitrogen balance be maintained. We have demonstrated in a previous communication<sup>5</sup> that nitrogen balance can be maintained in the diabetic, as in the normal, by the use of a diet containing 0.67 gm protein per day per kilogram of body weight, provided enough total calories are given to satisfy the metabolic needs. Protein much in excess of this minimum not only is not a necessity but is a disadvantage, for two reasons. As the protein content of a diet is decreased, the carbohydrate content may be increased without changing the glucose equivalent of the diet. Furthermore, with the decrease in the protein, there is a decrease in the fatty acids, and the food fat, with its greater energy value, may be increased without change in the ratio between the fatty acids and the glucose. For example, in a patient whose total glucose tolerance is 100 gm, either of the diets shown in Table 23

TABLE 23—CALORIC CONTENT OF DIETS EQUIVALENT IN GLUCOSE

	Protein	Fat	Carbohydrates	Calories	Fatty Acids	Glucose
1	150	130	0	1,770	186	100
2	50	180	55	2,040	185	100

may be fed without exceeding his glucose tolerance or changing the fatty acid content. The gain in calories is 270. In the second place, the specific dynamic action of the large amount of protein in the first diet causes a much larger increase in the expenditure of energy in excess of the basal rates than is caused by fat or carbohydrate, and thereby increases the inadequacy of the diet for maintenance. Recently Wilder, Boothby and Beeler<sup>20</sup> have found that high protein diets increased the basal metabolic rate of a diabetic patient as well as the post-absorptive rate. Wilder<sup>21</sup> believes that an excess of protein exerts a specifically depressant effect on the ability of the organism to utilize glucose.

*Total Caloric Content of the Diet.*—Besides the proportions of the individual foodstuffs in the diet, it is important to consider the total metabolism. This can conveniently be done by taking up the question under two heads, agreeing with the two phases of treatment: first, the period of desugarization, and second, the prolonged period of after treatment.

20 Wilder, R. M., Boothby, W. M., and Beeler, C. Studies of the Metabolism of Diabetes, *J. Biol. Chem.* **50** (Proc.) XXVIII, 1922.

21 Wilder, R. M. Optimal Food Mixtures for Diabetic Patient, *J. A. M. A.* **78** 1878 (June 17) 1922.

*Desugaring Period* —It is important to know whether desugaring is best accomplished by fasting, on the one hand, or by a sub-maintenance diet, on the other. As has been pointed out, fasting is not ideal for this purpose. A small proportion of patients die as the result of it, it does not always succeed in controlling glycosuria and acidosis, in some cases the fast must be terminated because of an increasing acidosis, and in all cases it is exhausting and a hardship for the patient. We have shown that in our series of adult cases a diet containing 15 gm protein, 90 gm fat, 12 gm carbohydrate and 960 calories has been uniformly successful in eliminating glycosuria and acidosis, without causing any deaths, and without great exhaustion of the patient. Among fifteen children less than 15 years of age treated by similar diets, none has failed to become sugar free, and none has developed an acidosis.

Fasting was introduced for the purpose of decreasing the work of that part of the pancreas that has to do with the intermediary metabolism of the food stuffs. Before accepting this method with its disadvantages it is important to analyze the effect of fasting on normal subjects. For this there is available a large collection of data. The fasting subject continues to require fuel for heat and energy, and derives this from his own tissues. Benedict,<sup>22</sup> for example, has analyzed the nature of the tissues used for this purpose, his subjects burned on the third day of their fast an average of the following amounts of the food stuffs per kilogram of body weight, protein, 1.28 gm, fat, 2.54 gm and carbohydrate, 0.36 gm. A man weighing 60 kg may, therefore, be expected to burn 77 gm protein, 152 gm fat, 22 gm carbohydrate, and 1820 calories.

In a general way, the fasting diabetic utilizes his body tissues in the same manner. There will be some variations in the actual proportions of the material burned from patient to patient because of differences in capacity for burning carbohydrate and differences in the ratios of fat to protein in the body. If body fat is available, the patient will derive most of his calories from its combustion. Voit<sup>23</sup> has shown that a well nourished dog which during starvation burned 96 gm of body fat, burned 97 gm when fed 100 gm fat. That is, the same amount of fat was burned, whether it came from his food or from his body. If, on the other hand, the subject is lean, more protein and less fat will be burned. A diabetic who has consumed most of his fat stores is thrown back on his body protein for his important source of energy. He may be spared some of this excessive

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<sup>22</sup> Benedict, F. G. Influence of Inanition, Carnegie Inst. Washington, D. C., Pub. 77, p. 476, 1907.

<sup>23</sup> Lusk, G. Science of Nutrition, Philadelphia, 1919.

endogenous protein metabolism by the addition to his metabolic mixture of ingested fat. In the well nourished diabetic, the food fat merely replaces part of the body fat that would be burned in fasting, in the lean diabetic the ingestion of fat permits the same sparing of protein which occurs in fasting in the well nourished diabetic because of the presence of fat stores. In our desugarization diet some of this endogenous protein is replaced. It is not certain that replacement of all protein would not have further advantages. The important fact to be derived from these considerations is that the starving subject continues to burn material, and in amounts not much smaller than when he is resting on a maintenance diet. The amount of relief for the pancreas by fasting must be relatively small. Not only does a diet containing 900 or 1000 calories not increase the work of the pancreas as regards internal secretions, but it may, perhaps, decrease it because it spares protein with its specific dynamic action on the metabolic rate.

We have cited examples of diabetic patients who did not become sugar free when fasted, but who did become sugar free when fed diets containing 900 calories derived chiefly from fat. That this might be predicted from the laws of metabolism has been pointed out by Woodyatt<sup>16</sup> and by us.<sup>5</sup> The lean diabetic who can burn little glucose and whose small residue of body fat supplies but little fuel is of necessity thrown back on his body protein for the production of heat and energy. This protein behaves in a manner no different from that of ingested protein, 58 per cent of it is converted into glucose. Because of the excessive destruction of body protein, glucose accumulates in the blood, hyperglycemia results, and the urine continues to show sugar. While this phenomenon, which at first glance appears paradoxical can easily be explained, it has been so completely disregarded in the past that it must be strongly emphasized. Protein derived from the tissues is just as capable of producing glycosuria as is protein assimilated from the intestinal tract.

The destruction of important body tissues during fasting cannot be ignored. Table 24 presented by Lusk<sup>23</sup> from the work of Kumagawa, shows the loss of weight of different organs of a dog during a twenty-four day fast. It is interesting to note that the greatest percentage of loss was in the pancreas. May it not be true that more harm than good is done? At any rate the damage to vital organs is not negligible.

A diet of 900 to 1000 calories derived chiefly from fat is devoid of most of the disadvantages of complete fasting for purposes of desugarization. It might be argued that such a diet has disadvantages of its own greater than those of the fasting method. It might be assumed that such a diet does not produce the depression of metabolism

which results from starvation, that it on the contrary causes an increase in the metabolic rate and that it adds glucose to the body

Data of the fall in basal metabolic rate of normal men due to fasting are available. Examination of Table 25 will show that a fall of less than 10 per cent of the total heat production of the first day occurred in five days. Unfortunately we have been unable to find enough studies of the effect of fasting on the basal metabolic rate of diabetics to justify any general statement. During five days of fasting, the basal metabolic rate of Cyril K<sup>24</sup> fell from 40.8 to 35.9 calories per square meter per hour—a decrease of 12 per cent. Studies of the metabolic rates of our patients have shown that there is a rapid fall in the metabolic rate, and that this fall is at least as great as that which may be expected from fasting.

TABLE 24—LOSS IN WEIGHT OF DIFFERENT ORGANS DURING STARVATION  
(KUMAGAWA)

Organs	Fat-Free Animal Contains in Percentage of Weight		Fresh Fat Free Organ Loses in Percentage Weight During a 24 Days' Fast
	Well Nourished	Starvation	
Skeleton	14.78	21.50	5
Skin	10.30	11.29	28
Muscles	53.77	48.39	42
Brain and cord	0.94	1.11	22
Eyes	0.11	0.16	3
Heart	0.54	0.69	16
Blood	7.14	5.69	48
Spleen	0.39	0.26	57
Liver	3.98	3.05	50
Pancreas	0.33	0.19	62
Kidney	0.66	0.45	55
Genitals	0.30	0.23	49
Stomach and intestine	5.81	6.02	32
Lungs	0.89	0.97	29

It is true, that the diet must cause some slight rise in the metabolic rate above basal. Since most of the energy, however, is derived from fat with its very low specific dynamic action, this rise is negligible.

The small amount of carbohydrate in the diet is compensated for by the decrease in glucose derived from protein consequent to the decrease in protein metabolism.

*Period of After Treatment*—Prolonged undernutrition has been advocated for rest of the weakened function of the pancreas. The disadvantages of this method have been pointed out. Its advocates believe that the resultant depression of the total metabolism stays the downward progress of the disease and even improves the carbohydrate

<sup>24</sup> Geyelin, H. R. and DuBois, E. F. Case of Diabetes Mellitus of Maximum Severity, J. A. M. A. 66:1532 (May 13) 1916.

tolerance in severe cases. It is undoubtedly true that the average duration of life of the diabetic has been increased materially during the last decade. It is impossible, however, to determine how much of this improvement has been due to undernutrition and how much to the increased interest in the disease, the more accurate measurement of the patient's food and his more thorough instruction in dietetics, consequent to the brilliant animal experiments of Allen and the painstaking clinical studies of Joslin. The demonstration that undernutrition is more effective in preventing downward progress and is more liable to improve carbohydrate tolerance than any other diet that keeps the patient aglycosuric has not been made. If it is true that a maintenance diet that will control glycosuria and acidosis will be as successful in the management of the disease as is undernutrition, it is apparent that the former is far more satisfactory than the latter. As has been pointed out, sufficient time has not elapsed for us to answer this

TABLE 25—EFFECT OF STARVATION ON TOTAL METABOLISM (IN CALORIES)

	Day					Percentile Fall on Fifth Day
	1	2	3	4	5	
"L" <sup>25</sup>	1,834	1,845	1,820	1,760	1,732	5.4
B F D <sup>22</sup>	2,109	2,103	2,110			
A L L <sup>22</sup>	1,956	2,174	2,056	1,971		
S A B (III) <sup>22</sup>	1,766	1,772	1,831	1,775	1,655	6.2
J A <sup>26</sup>	2,220	2,102	2,024	1,992	1,970	11.0
Cetti* <sup>27</sup>	1,618	1,618	1,618	1,618	1,504	7.1

\* Average for periods

question finally, but it is true that we have not as yet observed loss in tolerance in patients who have adhered to the diet as long as three years. The statistical study of our patients does not show a decrease in the duration of life when compared with other patients who have been treated for the same length of time by undernutrition.

#### CONCLUSIONS

A diet of 900 calories derived chiefly from fat produces the same fall in basal metabolic rate as does fasting. It has advantages over fasting in that it is more successful in desugarization and is a far less dangerous method.

A low protein, low carbohydrate, high fat, maintenance diet fed a large group of diabetic patients since March 1, 1918, maintained an

25 Benedict, F. G. A Study of Prolonged Fasting, Carnegie Inst. Washington, D. C., Pub. 103, 1914, p. 414.

26 Landergren, Souden and Tigerstedt. Skand. Arch. f. Physiol. **7**, 54, 87, 1897.

27 Lehmann, C., and Zuntz, N. Untersuchungen an Zwei hungernden Menschen, Arch. f. Pathol. Anat. **131** (Suppl.) 209, 1893.

aglycosuric state, was not attended by acidosis, maintained nitrogen balance, did not cause a hyperlipoidemia and was attended by its disappearance in those patients in whom it was present at entrance, supplied sufficient energy to avoid the evils of undernutrition and to permit an amount of activity compatible with earning a livelihood, and was, within the limits of our observation not attended by downward progress in uncomplicated cases

## A STEM-STATURE INDEX

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The ratio of the stem-length, i e, the sitting-height measured in a special and seemingly more accurate manner, to the stature is thought worth bringing to the attention of clinicians for the following reasons

1 The proportional sitting-height ( $100 S_1 - H$ ) has an established value among investigators of growth in school children and, indeed, in general, among physical anthropologists

2 The absolute measurements of sitting-height and the similar stem-length have been shown in the last six years to possess a notable parallelism to the body weight<sup>1 5</sup> Some have even believed this correlation to be closer than of weight to height<sup>1, 2</sup> At least, it seems fair to urge those who take any measurements to include the stem-length

3 The relationship of body trunk to extremities has, in the last three years, increasingly been brought forward by American physicians in regard to endocrine disease, especially of the hypophysis This relationship may, in our opinion, be best expressed by a stem-stature index ( $\lambda H$ ) Such a proposition has the following advantages (a) simplicity, since fewer measurements are needed than with the existing methods to be cited, (b) speed, for the same reason, (c) accuracy, since of the measurements heretofore suggested the stem has the most definite landmarks and also is the least vitiated by carelessness of position on the part of the subject, as has been indicated elsewhere<sup>2, 6</sup>

### THE STEM INDEX IN ENDOCRINE DISORDERS

Before illustrating the possible utility of this proposition, it will be well to survey the methods advocated by others

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1 Pirquet, C Sitzhöhe und Körpergewicht, System der Ernährung II, Ztschr f Kinderh **14** 211, 1916

2 Dreyer, G Investigations on the Normal Vital Capacity in Man and Its Relation to the Size of the Body, Lancet **2** 227 (Aug 9) 1919

3 Gray, H, and Root, H F Weight Prediction by the Formulae of Bornhardt, of von Pirquet, and of Dreyer, Boston M & S J **185** 28 (July 7) 1921

4 Gray, H, and Walker, A M Length and Weight, Am J Physical Anthropol **4** 231 (July-Sept) 1921

5 Gray, H, and Edmands, G H Indices of the State of Nutrition in Children, Am J Dis Child **23** 226 (March) 1922

6 Gray, H Sitting-height and Stem-length in Private School Boys, ibid **23** 406 (May) 1922



In 1912, Cushing's authoritative monograph<sup>7</sup> on the pituitary body affirmed that "the rôle of the hypophysis in growth is of primary interest" Such measurements, however, as were there reported shed little light on the proportional trunk to limb ratio under discussion Other writers, too, have evidently thought a ratio not worth consideration, but surely it is worth considering until it shall be either confirmed or condemned

In 1913, Friedenthal<sup>8</sup> displayed an elaborate geometric scheme including the skull height, neck length and Rumpflänge, which together he considered not very accurately equal to the sitting-height If we add his figures we can get 53.7, 17.7, and 12.4 respectively, which total 83.8 cm, and this divided by the average European height, 170 cm, yields 49 per cent for an index

In 1913, Tandler and Grosz,<sup>9</sup> while discussing eunuchoidism, gave values for Unterlänge, Oberlänge, and height As we have not discovered their technic we cannot compare their results strictly with others, but from the last two of their measurements we reckon an index (from their Figures 7, 8, 9 and 13) as varying from 41 to 45 and averaging 43.5 per cent This shows clearly the relative overgrowth of leg which they commented on in gonadal insufficiency

In 1916, Falta and Meyers<sup>10</sup> talked of the upper length as distance vertex to symphysis pubis (here to be abbreviated VSY), and the lower length variously as (a) symphysis to heels, or (b) anterior superior spine to internal malleolus, or (c) anterior superior spine to the floor No normal numerical index was there offered In their Observation 33, a subject with dyspituitarism, values were given from which the ratio VSY/H may be calculated as 35 per cent, a value agreeing with modern ideas of long legs in anterior lobe hyperfunction such as acromegaly

However, the pubis is too movable a landmark, as we have shown previously<sup>4</sup> This source of error receives support in a letter from a well known professor of neurology who has written on certain of these endocrine troubles He says "We do not believe that a few centimeters make very much difference The measurements are taken merely to get the general proportions" In other words, he has noticed that the measurements as taken by some are apt to be a few centimeters in error In fact, one of the papers cited gives lengths from

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7 Cushing, H. *The Pituitary Body*, Philadelphia, 1912

8 Friedenthal, H. *Ueber Wachstum*, *Ergebn d inn Med* **11** 688, 1913

9 Tandler, J., and Grosz, S. *Die biologischen Grundlagen der sekundären Geschlechtscharaktere*, Berlin, 1913

10 Falta, W., and Meyers, M. K. *Ductless Glandular Diseases*, Ed 2, Philadelphia, 1916, p 10

vertex to pubis and from pubis to floor whose sum differs from the total height by at least 2.5 cm in all of the four subjects reported, and in two of them by even 3.5 cm. Furthermore, the sum was greater than the height in two of the instances and in two was less, i. e., the error was not even constant in direction. Our own measurements to the symphysis have shown similar irregularities and, therefore, in our judgment bar the pubis as a landmark, convenient though it is to have the normal ratio an even 50 per cent.

In 1919, Timme<sup>11</sup> wrote

The bony structure in the first and second stages usually shows anomalies in proportionate skeletal growth, i. e., legs too long for thorax or vice versa. My scale for this determination is a fraction with the numerator as the distance from the sternoclavicular junction to the anterior superior spine of the ilium of the same side, and the denominator the distance from the anterior superior spine to the external malleolus, normally, this fraction is one-half—a larger one meaning too large a torso, while less than one-half represents too long a leg, I call this ratio the torso-leg ratio.

In 1920, Engelbach<sup>12</sup> and Tierney<sup>13</sup> likewise figured a 50 per cent torso-leg ratio, but with different landmarks. The upper measurement was taken from the top of the vertex, with the spine straightened out, to the top of the symphysis, with the patient in lying position. The "lower measurement" was taken from symphysis to sole.

In each of two cases of thyroid deficiency this ratio was 50 per cent, i. e., normal.

In five cases of hypopituitarism the range was from 48 to 51, averaging 49.6 per cent, indicating slightly longer legs than normal.

In two cases of hyperpituitarism the ratio came out 47 and 49, with an average of 48 per cent. This agrees with the usual expectation of long legs in acromegaly due to hyperpituitarism.

In one classical eunuchoid with ovarian insufficiency the ratio was 46 per cent. This conforms to the principle noted by Tandler and Grosz and to the indices we have calculated above from their data.

In 1920, Wilder<sup>14</sup> discussed the difficulty of measuring leg length. "In the leg there is no definite landmark to use as the proximal limit.

It is usual to consider the head of the femur as marking this limit, but here the difficulty is that this feature lies too deeply for palpation, or even approximately locating it."

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11 Timme, W. A New Pluriglandular Compensatory Syndrome, *M. Clinics N. America* 2:963 (Jan.) 1919.

12 Engelbach, W. Endocrine Amenorrhea, *M. Clinics N. America* 4:665 (Nov.) 1920.

13 Tierney, J. L. The Basal Metabolic Rate in Endocrine Disturbance, *M. Clinics of N. America* 4:775 (Nov.) 1920.

14 Wilder, H. H. A Laboratory Manual of Anthropometry, Philadelphia, 1920.

Since these things are so for an expert, how much truer for us physicians who practice anthropometry only on the side?

In 1921, Draper,<sup>15</sup> in his turn, practiced still another rule. His trunk length seems to correspond to stem-length. His technic is not detailed in the published paper, but seems of likely interest to any one working on this problem and is therefore quoted from a letter

In answer to your questions I may say that I have been somewhat dissatisfied in my own mind about the correctness of measuring the relation of trunk and body length by taking either the umbilicus or the symphysis as the point of division. I have been measuring as nearly as possible the actual length of the trunk and the actual length of the lower extremity. I have done this in the following way. By palpating the upper margin of the trochanter of the femur, and measuring from about a centimeter above this to allow for the slightly higher point of the head of the femur. From this I measure to the sole of the foot in one of two ways: either with the patient recumbent using an architect's T-square, hooking the cross piece under the foot and marking the trochanter point on the long arm of the T-square, or having the patient stand up against the wall and marking the trochanter point in the old-fashioned way against the wall. This gives the actual length of the lower extremity, at least in terms of its bone, which is what you are really after. In measuring the trunk I have felt that the actual information wanted was the distance from the tuberosity of the ischium (the point you really sit on) to the top of the head. This can be measured either by having the patient sit upon a hard stool with his back to wall or standing with his back to the wall and raising one thigh to the right angle position, then feeling for the tuberosity and making a mark on the wall, or you can do it also in a recumbent position with surprising accuracy by measuring from the same trochanter point used for the lower extremity measurement, to the top of the head. To this measurement must be added an average of ten or eleven centimeters because the acetabulum lies about that distance above the tuberosity.

The contours about the waist, hip, and thigh are often very misleading and so-called apparently long-waisted individuals actually measure out the other way and vice versa.

The normal torso-leg ratio he supposed to be about one to one.

In three cases of gonadal insufficiency which he reported, we figure the ratio as from 51 to 52, averaging 51.3 per cent, indicating rather short legs, which is contrary to the usual observations, as noted above.

In two cases with hyperovarian disease the ratio was 53 and 54 per cent. Here the short legs are what we should expect as the converse of Tandler and Grosz's long legs in castrates.

In 1921, Weisenburg and Patten<sup>16</sup> described a most systematic method for the investigation of pituitary disorders. For their torso-leg ratio, normally 1.2, as was the case with the different measurements of Timme, these writers took the distance from the suprasternal notch to the anterior superior spine (average, if different on the two sides),

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<sup>15</sup> Draper, G. Reversible Sex Phenomena, *M. Clinics N. America* 4:1345 (March) 1921.

<sup>16</sup> Weisenburg, T. H., and Patten, C. A. Methods of Investigation of Pituitary Disorders, *M. Clinics N. America* 5:759 (Nov.) 1921.

and from that spine to the internal malleolus. In their six dyspituitarism cases the ratio ranged from 45 to 67 per cent, with an average of 52, i e., a surprisingly long torso.

Krumbhaar,<sup>17</sup> in 1921, followed the same practice. The ratio in his cases of acromegaly (hyperprepituitarism) was 48 per cent, i e., a typically short torso.

Recently, Davenport and Love<sup>18</sup> discussed still other landmarks: "The pubic height is important because it is almost exactly (perhaps 35 mm. below) the level of the center of the acetabulum or the axis of the hinge of the femur the length of the physiological leg."

Here, again, we wish to insist that the pubic height is unreliable unless measured in a position more firmly defined than we have been able to find in the literature.

The "leg-length" gluteal fold to internal malleolus is not the physiological leg-length (and) is much less valuable than the total leg-length as indicated by the height of the pubic arch. The leg-length may also be secured by subtracting the sitting-height from the total stature.

These authors found the sitting-height about 53 per cent of the total height, but laid no great emphasis on this ratio. Incidentally, this proportion differs strikingly from the 50 per cent reported by most other observers.

Blumgarten<sup>19</sup> in 1922, like Falta and Meyers, took for the lower extremity the distance from the upper border of the pubis to the ground, and for the torso subtracted this distance from the height. In normals he found the torso less than the lower extremities.

The only acromegalic subject of whom we ourselves obtained measurements yielded the  $\lambda$  H index of 55 per cent, which is atypically above the 52 per cent which we show elsewhere to be normal. In other words, we found, like Weisenburg and Patten, that pituitary patients may have relatively short legs, contrary to what seems to be the rule, judging, for example, Falta and Meyers, Engelbach, Tierney, and Krumbhaar.

Since writing the foregoing, a review of 150 titles, mostly case reports on pituitary disease or on giantism with or without acromegaly, has revealed thirty-five articles containing measurements of trunk or extremities. In most instances there were no calculations of the ratio of the additional measurements to the stature, much less any normal index,

17 Krumbhaar, E. B. Pituitary Disorders, *M. Clinics N. America* 5:927 (Nov.) 1921.

18 Davenport, C. B., and Love, A. G. *Army Anthropology, Statistics, Medical Department U. S. Army in World War*, Washington, 1921, p. 199.

19 Blumgarten, A. S. The Rôle of the Endocrines in Common Medical Diseases, *M. Clinics N. America* 5:1023 (Jan.) 1922, and personal communications.

and owing to the variety of landmarks which were used the possible conclusions were less conspicuous than they might have been had a uniform method been used. For the sake of greater completeness the references are grouped according to the extra measurement recorded <sup>20</sup>

#### THE STEM-STATURE RATIO AND SIMILAR INDICES IN NORMALS

A synopsis of the rival ratios may be seen in the table. For the sake of compactness the following abbreviations have been assembled from the literature, and are listed in dictionary order.

C = cervicale, free end of the spine of the seventh cervical vertebra, the vertebra prominens (Wilder)

H = total height or stature

IS = iliospinalis anterior, anterior ventral spine of the crest of the ilium, old terminology anterior superior spine (Wilder)

<sup>20</sup> *Sitting Height*—Virchow *Ztschr f Ethnologie* **17** 469, 1885. Ammon, O. *L'anthropologie* **7** 285, 1896. Papillault, G. *Bull soc d'anthrop*, S 4 **10** 426 (June 1) 1899. Pittard. Personal communication quoted by Roy, P. These, Paris, Feb 25 1903, p 75. Launois, P. E., and Roy, P. *Rev neurol* **10** 1054 (Nov-Dec) 1902, and *Nouv Icon* **15** 540 1902, and *Compt rend soc biol* **55** 22 (Jan 10) 1903, and *Etudes biologiques sur les geants*, Paris, 1904. Pittard, E. *L'anthropologie* **14** 463, 1903. Luschan *Ztschr f Ethnologie* **35** 479, 1903. Redlich, E. *Wien klin Rundschau* **20** 489 and 508 (July 1) 1906. Widal and Bordin. *Bull et mem Soc med d hôp de Paris*, S 3 **22** 740 (Oct 13) 1905. Levi, E. *Nouv Icon* **21** 297 and 441, 1908. Levi, E., and Franchini, G. *Nouv Icon* **22** 449 (Feb 5) 1909.

*Great Trochanter to Ground*—Virchow 1885, loc cit. Brissaud, E., and Meige, H. *J de med et de chir pratique* **66** 49 (Jan 25) 1895. Hutchinson, W. *Am J M Sc* **110** 190 (Aug) 1895. Papillault, G. *Bull et mem Soc d'anthrop*, S 5 **3** 393 (May 1) 1902. Buday, K., and Jansco, N. *Deutsch Arch f klin Med* **60** 385 (June 16) 1898. Launois and Roy loc cit, 1902 1903 1904. Huchard, H., and Launois, P. E. *Bull et mem Soc med d hop de Paris*, S 3 **20** (Dec 11) 1903. Levi loc cit, 1908. Thibierge, G., and Gastinel, P. *Nouv Icon* **22** 442 (Feb 5) 1909.

*Great Trochanter to Malleolus*—Papillault loc cit, 1902. Wieting, J. *Deutsch med Wehnschr* **29** 371 (May 21) 1903. Huchard and Launois loc cit. Duckworth, W. L. H. *J Anat & Physiol* **41** 30 (Oct) 1906. Pel, P. K. *Nouv Icon* **19** 76, 1906. Levi 1908, 1909, loc cit.

*Anterior Superior Spine of Ilium to Ground*—Fritzsche and Klebs. *Klin u pathol anat Untersuchungen*, Leipzig, 1884. Marie, P. *Nouv Icon* **1** 173, 1888. Papillault 1902 loc cit. Luschan 1903, loc cit. Pel, P. K. *Berl klin Wehnschr* **42** 25 (Oct 30) 1905. Levi 1908, loc cit.

*Anterior Superior Spine of Ilium to Malleolus*—Sainton, P. *Nouv Icon* **15** 272, 1902. Hudovernig, C., and Popovits, U. P. *Nouv Icon* **16** 181 (May-June) 1903. Traschio, G. B. *Atti della soc romana di antropologia* **9** 95, 1903.

*Iliac Crest to Ground*—Virchow 1885, loc cit. Dana, C. L. *J Nerv & Ment Dis* **20** 725 (Nov) 1893. Hutchinson, W. *New York M J* **67** 452 (March 12) 1898.

*Top of Symphysis Pubis to Ground*—Tandler, J., and Grosz, S. *Wien klin Wehnschr* **21** 277 (Feb 27) 1908, and *Arch f Entwicklungsmechanik* **27** 35 (Jan 12) 1909, and **30** Part II, 236 (June 14) 1910, and **29** 290 (July 12) 1910.

$\lambda$  = stem-length, vertex to ischial tuberosities (Walker, Dreyer)

$S_1$  = sitting-height (Pirquet)

SPH = spherion, lowest point of internal malleolus (Wilder)

SST = suprasternale, the middle of the suprasternal notch in the upper margin of the sternum (Wilder), called by others the jugulum, sternion, incisura sternalis

SY = symphysis (Wilder), cephalad edge of middle of symphysis pubis

TRO = trochanterion, a point of some uncertainty and never very precise It is defined as the highest point upon the trochanter major (Wilder)

V = vertex (Wilder)

In our own series of eighty healthy men, aged 18 to 71 years, mostly 20 to 35, the index  $100 \lambda - H$  ranged from 48 to 55 and averaged 51.6 per cent The frequency of each index was as follows

$$100 \lambda/H = 48-49-50-51-52-53-54-55$$

$$No = 3-5-12-17-18-18-5-2 = 80$$

#### NORMAL BODY TRUNK INDICES ACCORDING TO DIFFERENT AUTHORS' DEFINITIONS AND OBSERVATIONS

Measurements	Author	Material	Percentage	
			Range	Average
VSY - H	Quetelet, 1871	Belgians	48-50	49
	Gray and Walker, 1921	U S	48-52	50
	Davenport and Love, 1921	U S soldiers	49.9-50.7	50.5
(Sternoclavicular junction to IS) - (IS to external malleolus)	Timme, 1919	U S		50
(SST to IS) - (SST to IS + (IS to SPH))	Weisenburg and Patten, 1921 Krumbhaar, 1921	U S		50
		U S		50
$S_1 - H$	Friedenthal, 1913 Davenport and Love, 1921 Baldwin, 1921	German		49
		U S soldiers		52.6
		U S children		
	Gray, 1922	Age 6		55.7
		Age 13		52.0
		U S children		
		Age 6, 7		54.6
		Age 8 and 9		52.1
		Age 10 and 11		51.3
		Age 12 and 13		51.1
		Age 14, 15 and 16		50.8
		Age 17 and 18		50.0
	Draper, 1921			50
$\lambda - (\lambda + \text{TRO to sole})$	Gray, 1922	U S children		
$\lambda - H$	Gray, 1922	Age 6 and 7		53.7
		Age 8 and 9		51.6
		Age 10 and 11		50.9
		Age 12 and 13		50.0
		Age 14, 15 and 16		49.1
		Age 17 and 18		49.0
	Gray, 1923	U S adults		51.6
(H minus distance gluteal fold to SPH) - H	Davenport and Love, 1921	U S soldiers		58.3

THE STEM-STATURE INDEX AS A GAGE OF STAMINA  
IN VARSITY OARSMEN

We have been interested in the belief credited to Ruschenberger of the U S Army by Hitchcock<sup>21</sup> in 1893, that the length of the cerebrospinal column may be more dependable than total stature in estimating physical vigor. Ruschenberger conjectured that, as a rule, men of average height made up of a long trunk and comparatively short legs possess greater endurance for labor and exposure to vicissitudes of all kinds than men with comparatively long legs and short trunk.

In order to illuminate this question, we hit on the notion of measuring men of superior sturdiness, irrespective of mere strength or beauty of build. Rowing men seem to us to fulfill this requirement. Among our eighty normals, therefore, are included thirty-six oarsmen,<sup>22</sup> nearly all measured at the Harvard crew quarters at Red Top in June, 1921. Their average index was 51.3, against 51.8 for the forty-four noncrew controls. The difference, 0.50, seems insignificant. However, such small differences are sometimes legitimately regarded as significant when analyzed by the modern biometric methods of Karl Pearson's school. Now then the probable errors, 0.1679 and 0.1655, for the respective means ( $m_1$  and  $m_2$ ) just given can be substituted in the formula  $P_{m_1 m_2} = \sqrt{(P_{m_1})^2 + (P_{m_2})^2}$  thus finding the probable error of the difference ( $P_{m_1 m_2}$ ) to be 0.236. Now the difference ( $m_1 - m_2$ ) of 0.50 is only 2.1 times this, its probable error, and is, therefore, hardly significant. In other words, stamina is apparently unrelated to a relatively long trunk. It is still possible that a larger series might show a difference 2.5 times the probable error, in which case the conclusion would be permissible that a man with relatively long legs is more apt to be a fit oarsman than a man with a long trunk—contrary to our original notion.

#### SUMMARY

The ratio of the stem-length (or the sitting-height) to the stature is thought to be worth consideration by clinicians.

This stem-stature index and other torso-leg ratios are discussed with reference to skeletal anomalies in diseases of internal secretion.

This  $\lambda$  H index is also tested as a possible measure of stamina.

32 The Fenway

<sup>21</sup> Hitchcock, E. The Anthropometric Statistics of Amherst Coll., Quart. Pub. Am. Statistical Assn. 3: 596 (Dec.) 1893.

<sup>22</sup> For the measurements on the crew men I am greatly indebted to Dr. George P. Denny.

# ALBUMINURIA ITS CLINICAL SIGNIFICANCE AS SHOWN BY CHEMICAL STUDY OF THE BLOOD\*

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Although many tests of kidney function have come into prominence and waned to insignificance, albuminuria has long been a simple criterion of abnormality. But albuminuria is not a sure indication of damaged kidneys, for it may appear when these organs are normal, as in orthostatic albuminuria,<sup>1</sup> or it may be absent in a wide spread degeneration of the kidneys, as in interstitial nephritis. Furthermore, as will be pointed out in this paper, albuminuria may be excessive from passive congestion of the kidneys, the primary difficulty being in the heart. When albuminuria is excessive and associated with oliguria and apparent uremia,<sup>2</sup> as a late event in arterial hypertension, or in circulatory failure, it may cause much apprehension, on the other hand, the absence of albumin in the urine may give a false sense of security.

The nephroses of acute infection or resulting from focal infection, are associated with albuminuria,<sup>3</sup> more or less severe, the damage may be transient, fulminating or permanent.<sup>4</sup>

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\* Albuminuria as here referred to is associated with casts in varying abundance. Albuminuria resulting from pyonephrosis or inflammatory conditions in the urinary tract are not considered, since their recognition is obvious.

1 One observer estimates the frequency of orthostatic albuminuria as high as 19 per cent in adolescents, many losing this tendency as they grow older.

2 Attention is directed to uremic symptoms resulting from cerebral edema, the latter being due to circulatory changes largely, and disappearing on adequate cardiac stimulation, as shown in a woman, aged 52, who had been stuporous and semicomatose for eight days with marked albuminuria and oliguria. Lumbar puncture showed increased pressure and a high urea content of the spinal fluid. The removal of spinal fluid and stimulation for the dilated, uncompensated heart seemed to start recovery. She was well for five years and died of intercurrent carcinoma of the stomach, during this period there was very little evidence of kidney involvement. That edema of the brain may occur in uremia is stated by N B Foster (Uremia, J A M A 76 281 [Jan 29] 1921) as follows: "In its greatest severity edema of the brain occurs in but one type of uremia, that type in which stupor and coma without convulsions, without psychic or motor disturbances, is the prominent nervous symptom." For a clear discussion of uremia, as modernly understood, and cerebral edema, the reader is referred to Foster's paper.

3 George Baer and H Lande (Glomerulonephritis as a Complication of Subacute Streptococcus Endocarditis, J A M A 75 789 [Sept 18] 1920) report twenty-seven cases of subacute streptococcus endocarditis in which nine patients died of uremia due to intercurrent glomerular nephritis or its sequel, chronic diffuse nephritis. They found that scarlet fever, acute and chronic streptococcus angina and streptococcus endocarditis are frequently complicated by acute glomerular nephritis.

(Footnote 4 on next page)



Nonnephritic albuminuria,<sup>5</sup> including "physiologic," "transient," "functional," "adolescent," "intermittent" and the albuminuria in pregnancy, etc., is a large group comparatively easy of detection. The difference between physiologic and pathologic albuminuria is quantitative, not qualitative, and the term "albuminuria" implies that serum albumin is present in the urine in such quantities that it can be detected by the not very delicate tests accepted as standard (as the heat and acid test).<sup>6</sup>

From the foregoing, it is readily seen that dependence on urinary findings alone leads to error. Furthermore, as stated by McLester,<sup>7</sup> many persons show albumin and casts in the urine for years, without any other signs of nephritis, while at the same time, they demonstrate their ability to withstand, without injury, all kinds of fatigue and hardships. Such people cannot be said to have nephritis. He also points out that chronic nephritis can be divided sharply into two groups, (1) the type with edema, and (2) that without edema. The latter is not a disease of the kidneys alone, for in the resulting disturbed physiology, other organs, notably the heart and arteries, play an equally important part, and in the last analysis it is the efficiency of these other organs which determines, as a rule, the fate of the patient.

#### RENAL FUNCTION TESTS

Discussion of albuminuria leads to a consideration of renal function. In attempting to explain the albuminuria as seen in the cases cited below, various methods which have been used in the last decade were reviewed

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4 Eli Moschowitz (Hypertension, Its Significance, Relation to Arteriosclerosis and Nephritis and Etiology, *Am J M Sc* **168** 668 [Nov] 1919) is of the opinion that gross injury of the kidney parenchyma perhaps plays the greatest role in albuminuria of the acute infections, but that it (injury of the parenchyma) is not a factor of much importance in albuminuria associated with hypertension and also points out (*ibid* p 684) that albuminuria is not necessarily the result of injury (even profound) of the kidney and that badly diseased kidneys may show no albuminuria.

5 R L M Wallis (Nonnephritic Albuminuria, *Proc Roy Soc Lond Sect Med* **13** 96, 1920), in discussing proteinuria not due to organic disease of the kidney, including physiologic, transient and intermittent albuminuria, and a group he designates as "leaky kidneys," points out that all ordinary tests for albumin are for serum albumin. In the group under discussion, the chemical examination of the blood shows no retention. Physiologic albuminuria is the result of serum albumin leaking through the kidneys, with excessive amounts of urinary constituents (after exercise, cold baths, alimentary causes, etc.). In functional albuminuria there is no relation to food or exercise as seen in adolescent, cyclic and postural albuminuria. A third group of "leaky kidneys" is a long standing proteinuria, and there is no evidence of kidney disease, or if present, it is not progressive. The chief protein in nonnephritic albuminuria is euglobulin associated with lipoids.

6 Emerson Clinical Diagnosis, J B Lippincott, 1921, p 224

7 McLester, I S Treatment of Chronic Nephritis Without Edema, *J A M A* **77** 88 (July 9) 1921

and used to some extent. Methods using the urine alone as the object of examination were found to be disappointing, the chemical examinations of the blood along with a renal test diet being found most valuable in determining the state of kidney function.

Normal renal function depends so largely on the volume of blood passing through the kidneys, that they respond readily to blood flow and blood pressure. These organs differ from all other secreting glands in their intimate relation to the general circulation, a rise in blood pressure is accompanied by an increase in urine flow unless there is a simultaneous vasoconstriction in the kidneys, and a fall in blood pressure is followed in general by decreased urine flow unless the renal vessels are dilated. The determining factor is the capillary pressure in the glomerulus—not the general vascular pressure.

The modern view of secretion of the urine accepts Ludwig's <sup>8</sup> scheme of filtration through the capsules and the "vital secretion" of Heidenhain. Filtration is purely physical, reabsorption in the tubule requires a healthy cell. The function of the kidney is the filtration of non-colloidal constituents of the blood through the glomerulus and absorption of this fluid through the tubule cells, the capsule furnishes fluid as it is the circulation and the tubule returns to the blood the fluid best adapted to the tissues,<sup>9</sup> allowing the rest to escape in the urine.<sup>10</sup>

Albuminuria may be produced experimentally by interrupting the blood supply by compressing vein, artery or ureter. If the artery is clamped for thirty seconds, secretion stops completely and is reinstated after an hour or so, the urine contains abundant protein at first and ultimately resumes its normal character. This is due to alteration in the permeability of the capsule by asphyxia so that it permits the passage of the proteins of the blood.

Since the urine is the excretory product of renal activity, estimation of renal function has been attempted through urine tests. Estimation of urinary nitrogen, chlorids, diastase, urea, uric acid, the power of the kidney to eliminate foreign substances, cryoscopy, its electrical conductivity, experimental polyuria, etc., have been disappointing, for the elimination of urine is complicated, depending on many factors beyond

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8 Cushny, A. R. *The Secretion of the Urine*, London and New York, Longmans, Green and Co., 1917, p. 101.

9 Cushny, A. R. *The Secretion of the Urine*, New York, Longmans, Green & Co., 1917, p. 47.

10 According to Cushny, casts are chiefly composed of albumin passing through the kidney capsule, enriched by the detritus of degenerating tubule cells, but Christian (*Am J M Sc* **161** 625 [May] 1916) thinks they originate from degenerated epithelium, the granular being young and the hyaline older.

accurate control, such as the state of circulation, food and fluid intake, and psychic and nervous conditions<sup>11</sup>

Following the work of Schlayer<sup>12</sup> and others who attempted clinically to classify nephritis as tubular, glomerular and vascular (through the readiness with which water and lactose pass through the glomeruli, and potassium iodide and sodium chloride through the tubules), many attempts were made to make clinical and histologic nephritis conform. These have failed to give adequate information, and even Ambard's coefficient (the relation between urinary and blood urea) is unsatisfactory because of these variable factors in urine elimination. Further, the disease process in the kidney is rarely confined to one structure, but is diffuse.

The excretion of dyes (methylene blue, indigocarmine, phenolsulphonaphthalein, etc.), offers a simple clinical method of estimating renal activity, but here again one must bear in mind the many factors concerned in their elimination, and that prostatic obstruction or passive hyperemia of the kidneys may produce a low excretion of these substances<sup>13</sup>

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11 The readiness with which the kidneys eliminate an excess of any urinary constituents is utilized in giving urea, 15 gm, while the diet is kept fairly constant and the rate and amount of excretion is measured as described by Addis, McCaskey, McLean and De Wesselow. Recently Weiss (Weiss, E. The Urea Concentration Test for Kidney Function, *J A M A* **76** 298 [Jan 29] 1921) has added to this the estimation of the blood urea nitrogen with a review of the literature. Uric acid has been used in the same way by Upham and Higley and Magath. More recently T. L. Squier and L. H. Newburgh (Renal Irritation in Man from High Protein Diet, *Arch Int Med* **28** 1 [July] 1921) have used high protein diets, attempting to obtain evidence in hypertension cases of disturbed kidney function by throwing an extra load on the kidneys. This was followed by albuminuria and casts and the presence of red corpuscles in the urine. There was no effect on blood pressure.

12 Hedinger and Schlayer. *Deutsch Arch f klin Med* **114** 120, 1914.

13 Thayer, W. S., and Snowden, R. R. Comparison of the Results of the Phenolsulphonaphthalein Test of Renal Function with the Anatomic Changes Observed in the Kidneys at Necropsy, *Am J M Sc* **148** 781 (Dec) 1914.

J. H. Agnew (A Comparative Study of Phthalein and Incoagulable Nitrogen of the Blood in Cardiorenal Disease, *Arch Int Med* **13** 485 [March] 1914) stated that when phenolsulphonaphthalein was below 40 per cent the blood nitrogen was definitely increased.

Rowntree and his co-workers (Rowntree, L. G., Marshall, E. K., and Baetjer, W. A. Further Studies of Renal Function in Renal, Cardiorenal and Cardiac Diseases, *Arch Int Med* **15** 543 [April] 1915) studied diastase, phenolsulphonaphthalein, cryoscopy, total nitrogen and urea of the blood, finding diastase low in mild and severe nephritis. In cardiac and cardiorenal cases the findings were bizarre, phenolsulphonaphthalein was then thought by them to be the test of choice, but "whenever phenolsulphonaphthalein is decreased, even slightly, the total N or blood urea, or both, should be determined."

Renal test diets as suggested by v Monakow in 1911, Hedinger and Schlayer in 1914 and as modified by Mosenthal,<sup>14</sup> Christian,<sup>15</sup> O'Hare<sup>16</sup> and others offer simple clinical means of estimating renal function through measuring the concentrating power of the kidney

Mosenthal<sup>14</sup> has now modified his former method based on the observations of Hedinger and Schlayer in 1914, using an American standard diet and only one day of measured diet, covering the period of urine collections. It is applicable to the ambulatory patients and allows usual food and routine. The urine is collected at two hour intervals, only one direction being insisted on, that the night urine be collected at a time beginning three hours after supper and no sooner.

Normal renal activity is characterized by variations in specific gravity up to 1.020 in the two hour test. A high fixed gravity may be

TABLE 1 — RENAL TEST DIET SHOWING VARIATIONS IN URINE OUTPUT, SPECIFIC GRAVITY, NITROGEN AND CHLORIDS IN NORMAL (N) AND NEPHRITIC (NEPH) URINES (AFTER MOSENTHAL)

Hour	Renal Test Diet							
	Amount, Cc		Specific Gravity		Sodium Chlorid, Gm		Nitrogen, Gm	
	Normal	Nephritic	Normal	Nephritic	Normal	Nephritic	Normal	Nephritic
8-10	315	102	1.006	1.017				
10-12	128	90	1.014	1.020				
12- 2	120	98	1.017	1.020				
2- 4	122	118	1.020	1.021				
4- 6	76	88	1.022	1.020				
6- 8	100	390	1.027	1.006				
Total day	861	886			6.71	3.86	6.80	4.62
Total night	248	1,280	1.025	1.010	1.71	6.26	3.05	4.86
Total 24 hours	1,109	2,166			8.42	10.12	9.85	9.48
Intake	1,760	1,760			8.50	8.50	13.40	13.40
Balance	+650	-406			+0.08	-1.62	+3.55	+3.92

seen in normal persons because they take too little fluid, or may occur in disease characterized by edema and oliguria, as myocardial insufficiency, acute or chronic nephritis. A low fixed gravity is found in chronic nephritis, diabetes insipidus, marked anemia, the elimination of edema, pyelitis, polycystic kidney, poststatic hypertrophy, etc. Such patients do well as long as polyuria compensates for the lack of power to concentrate. The normal total quantity should be 400 c c less than the intake and 750 c c or less is secreted at night, a larger amount may indicate that the kidney is putting forth a greater effort than it

14 Mosenthal, H. O. Renal Function as Measured by the Elimination of Fluids, Salt and Nitrogen, and the Specific Gravity of the Urine, *Arch Int Med* **16**:733 (Dec.) 1915, *ibid* **22**:770 (Dec.) 1918.

15 Christian, H. Some Phases of the Nephritis Problem, *Am J M Sc* **151**:625 (May) 1916. Tests for Measurements of Renal Efficiency in Relation to Prognosis in Nephritis, *Penn M J* **21**:233 (Jan.) 1918.

16 O'Hare, J. P. Renal Function in Vascular Hypertension, *Boston M & S J* **132**:345 (April) 1920.

normally should. This overstrain may cause damage if continued indefinitely. In passive congestion water and salt are diminished while the nitrogen remains approximately normal. In the contracted kidney nitrogen and salt are retained. Hypertensive nephritis is characterized by nocturnal polyuria, a tendency to total polyuria, fixation of specific gravity, fixation of two hourly quantity and retention of salt and nitrogen (Table 1).

Another avenue of approach in the estimation of renal function is the chemical examination of the blood<sup>17</sup> for retention of substances normally excreted by the kidneys, particularly urea, uric acid, and creatinin. Blood sugar may also be increased in interstitial nephritis.<sup>18</sup> Since creatinin is readily excreted through the kidneys, urea less readily and uric acid least readily, it was shown by Meyers and Killian<sup>19</sup>

TABLE 2—THE BLOOD IN NEPHRITIC AND CARDIAC ALBUMINURIA SHOWING NORMAL VALUES FOR NONPROTEIN NITROGEN, UREA, URIC ACID, CREATININ AND SUGAR AS COMPARED WITH FINDINGS IN PASSIVE RENAL CONGESTION OR NEPHRITIS AS SHOWN BY GETTLER, GRADWOHL, MEYERS AND FINE

	Nonprotein Nitrogen, Mg	Urea Nitrogen, Mg	Creat inin, Mg	Uric Acid, Mg	Sugar, Mg
Normal	25-40	10-15	1-2	1-3	0.08-0.11
Gettler					
Nephritis (600 cases)	40-460	20-275	2-42	3-17	0.075-0.375
Cardiac (350 cases)	35-220	18-180	15-12	2.5-7	0.07-0.135
Gradwohl					
Nephritis (4 cases)		21-108	2.15-4.48	5.9-9.8	0.09-0.188
Cardiac (4 cases)		11-16	0.9-2	2.4-3.3	0.096-0.155
Meyers and Fine					
Chronic nephritis	30-80	15-50	1-3	1-4	
Uremic nephritis	120-350	80-300	4-34	4-15	0.10-0.20

that a marked retention of blood creatinin is of serious prognostic import. Upham and Higley<sup>20</sup> and Magath<sup>21</sup> and others fed uric acid as a test of renal insufficiency.

17 So much work has been done in this line in the last decade that it is hardly necessary to refer to the investigations of Folin and Dennis, Benedict and Lewis, Meyers and Fine and Christian and others who have opened the way for the clinical application of experimental physiologic chemistry.

18 J. R. Williams and E. M. Humphreys studied fifty cases of cardiorenal disease, finding the blood sugar varying from 0.06 to 0.25 per cent, and varying directly with the severity of the disease. (The Clinical Significance of Blood Sugar in Nephritis and Other Diseases, Arch Int Med 22:537 [May] 1919.) They quote Hopkins, who in 1915 studied twenty-six cases of nephritis, finding the blood sugar normal in only five, also Meyers and Bailey, who in 1916 studied eleven cases, finding blood sugar from 0.10 to 0.20 per cent.

19 Meyers, V. C., and Killian, J. A. The Prognostic Value of Creatinin of the Blood in Nephritis, Am J M Sc 157:674 (May) 1919. Meyers, V. C., and Lough, W. G. The Creatinin of the Blood in Nephritis. Its Diagnostic Value, Arch Int Med 16:536 (Oct) 1915.

20 Upham, R., and Higley, H. A. Study of Renal Concentration Power for Uric Acid in Early Chronic Interstitial Nephritis, Arch Int Med 22:537 (Sept) 1920.

21 Magath, T. B. A Test for Renal Insufficiency, J Lab & Clin Med 6:463 (May) 1921.

While diseased kidneys interfere with the excretion of these substances, causing them to be retained in the body,<sup>22</sup> passive renal congestion does not do so, as shown in the accompanying tables and case reports, and as pointed out by Gradwohl and Powell,<sup>23</sup> Christian,<sup>24</sup> Williams<sup>25</sup> and others (Table 2)

From the foregoing consideration of various renal function tests, it will be seen that groping, tedious effort and painstaking accumulation of laboratory data have at least given a clearer conception of the difficulties in establishing any one test for kidney efficiency. While most of the older methods of examination of the urine have been given up for reasons already cited, albumin and casts are easily found by any one, and immediately arouse suspicion of disturbed renal activity, they give a clue also as to the degree of this disturbance, but hardly of the extent of damage.

One is often surprised to find that patients who at first suggest the "cardionephritis syndrome" are suffering more from circulatory weakness than nephritis, for oliguria, edema, excessive albuminuria, and even apparent mild uremia improve with improved circulation. Again, patients with arterial hypertension show "nephritic" symptoms from time to time, which are due to myocardial weakness.

In considering the cases studied from the standpoint of albuminuria the following table is submitted for the differentiation of primary (or renal) from secondary (or extrarenal) albuminuria.

1 *Primary*—With definite evidence of renal insufficiency and probable permanent damage (nephritis)<sup>26</sup>

2 *Secondary*—Due to extrarenal factors (a) Nonnephritic albuminuria (physiologic, adolescent, functional, etc.), (b) in cardiac

22 That nitrogen is not retained exclusively in the blood is shown by N. B. Foster (The Increased Extract Nitrogen in the Tissues, with Chronic Nephritis, *Arch. Int. Med.* **24** 242 [Aug.] 1919).

23 Gradwohl, R. B., and Powell, C. The Usefulness of Blood Chemistry Methods in the Differential Diagnosis and Cardiac and Renal Diseases, *Southern M. J.* **11** 335 (May) 1918.

24 Christian, H. A. The Use of Renal Function Tests in Cases of Nephritis, *J. Urol.* **1** 319 (June) 1917.

25 Williams, J. L. The Total Nonprotein Nitrogen Constituents of the Blood in Chronic Nephritis with Hypertension, *Arch. Int. Med.* **28** 426 (Oct.) 1921. Williams found that in hypertension and uremia the nonprotein nitrogen was increased and phenolsulphonaphthalein excretion decreased. Cardiac insufficiency without nephritis is associated with moderate retention of nonprotein substances of the blood, especially of uric acid. He says the presence of albumin and casts do not necessarily suggest nephritis but that improvement in the circulation is accompanied by decrease in nitrogenous extract in the blood, especially of uric acid.

26 C. P. Emerson (The Acute Element in the Nephropathies, *J. A. M. A.* **77** 745 [Sept. 3] 1921) considers that nephritis, when well established, is not a chronic process but due to repeated acute attacks. In the albuminuria due to extrarenal factors, especially from passive congestion, it is conceivable that permanent damage may result from repeated attacks.

decompensation with resultant passive congestion (oliguria, edema, uremic symptoms)

1 With valvular lesions (rheumatic, syphilitic, or sclerotic), with myocardial weakness and dilatation

2 Resulting from long continued vascular hypertension and final cardiac breakdown

#### DISCUSSION OF CLINICAL GROUPS

In studying the results of functional tests, and especially of blood chemistry in patients having albuminuria, those with vascular hypertension form one group, and the others have been studied as a miscellaneous group. In the former, the following points stand out (1) these patients at sometime or other show "cardionephritic" symptoms. It will be seen that albuminuria varies greatly in the same patient, as do other evidences of renal embarrassment, and that there is often a definite relationship between cardiac breakdown and the nephritic symptoms (Table 3). (2) The predominating symptoms in hypertension express themselves as (a) cerebral, (b) cardiac, or (c) nephritic, appearing singly, or jointly. (3) In these patients, the chemical examination of the blood was of diagnostic value.

Some of the hypertension cases have been seen more or less regularly over a period of years (from five to eight). Since making chemical examinations of the blood one has the impression of assurance of the true state of the kidneys which formerly was doubtful.

Uric acid<sup>27</sup> values have been high in some cases, as in 17 K (5.75), 21 J L (5.75, 6.25 and 6.7) and 85 H (4.1), but at such times there was no particular change in the patient's general condition.

The alkali reserve was estimated in seven instances and was not of any particular help in the care of the patients.

Blood sugar was not high, as a rule. Case 29 H showed 0.204 in September, 1919, but there was no glycosuria, while Cases 45 F (0.12), 17 K (0.142 and 0.125) and 14 W (0.14) showed higher values than normal.

#### REPORT OF CASES

*Hypertension Cases with Albuminuria (Table 3)* — The following cases illustrate the points that have already been made, some are given at considerable length because they are typical of recurring albuminuria secondary to cardiac decompensation and resultant static changes (passive congestion) in the kidneys<sup>27a</sup>

<sup>27</sup> All chemical methods were standard and done with the helpful advice of Professor Haskins of the Medical Department of the University of Oregon. Blood was obtained in the morning, the patient fasting.

<sup>27a</sup> Measurements of enlarged heart are to left of midclavicular line. Quantitative albumin is in parts per thousand by Esbach's method.

TABLE 3—HYPERTENSION GROUP SHOWING INCREASE IN ALBUMINURIA OFTEN COINCIDENT WITH INCREASED CARDIAC EMBARRASSMENT  
CARDIAC SYMPTOMS WERE DYSPNEA, RAPID PULSE, INCREASED HEART BORDERS, CYANOSIS, ENLARGED LIVER, EDEMA, ETC CEREBRAL  
SYMPTOMS VARIED FROM MENTAL CONFUSION, HEADACHE, SCLEROTIC RETINAL VESSELS, APHASIA OR CEREBRAL HEMORRHAGE NEPHRITIC  
SYMPTOMS WERE OLIGURIA, MARKED ALBUMINURIA AND CASTS, EDEMA, UREMIA SYMPTOMS

Case	Age	Date	Predominating Symptoms			Blood Pressure	Blood Chemistry				Urine			
			Cerebral	Cardiac	Nephritic		Urea	Uric Acid	Great-min	Sugar	Alkali Reserve	Specific Gravity	Albu min	Casts
45 F	51	4/12/20		++	++	210-135	15	2.17	1.4	0.12		1.016	++	++
		4/14/20		++	++	210-155	14	2.62	1.17	0.11		1.009	0.1%	++
		5/1/20		+	±	195-135	16	3.12	2	0.10		1.010	+	+
		12/1/20		++	++	195-130						1.014	0.35%	++
81 S	58	2/4/21	++	++	++	150-110						1.020	++	++
		6/1/20		++	++	155-125						1.020	++	++
		9/1/20	++	++	±	170-90	15	2.75	1.9	0.08	62	1.010	+	+
50 C	50	3/1/20	++	++	++	180-140	12.5	1.25	2.2	0.083	72	1.012	++	++
		6/1/20	+	++	++	225-150						1.020	++	++
		8/1/20	++	++	+	250-110	10	2.74	2.43	0.089	70	1.018	++	++
71 G	74	6/12/20	++	+	++	185-105	12.5	2.92	2			1.018	++	+
6 J	59	6/14/20	++	++	+		13.5	2.5	1.83	0.083		0.2%	++	+
17 K	70	5/1/19	++	±	+	240-120	11		1.16	0.09		1.020	+	+
		7/1/19	++	±	±	180-165						1.020	±	±
		8/1/15	++	±	±	280-142	25.5	2.37	2	0.142		1.015	±	±
		8/1/19	++	±	±	225-138			1.17			1.018	±	±
		1/1/20	++	±	±	220-130			1.7		70	1.018	±	±
		6/1/20	++	±	±	240-135	14.5	5.75	1.9	0.125		1.017	±	±
		8/1/21	++	++	+	139-45	30.5		1.9	0.11		1.015	±	±
21 J L	69	4/1/14	+	++	++	205-130						1.018	++	++
		9/1/19	++	++	++	190-105	27		4	0.10		1.013	++	++
		10/1/19	++	+	+	210-125	22.5		2	0.12		1.012	+	+
		5/1/20	++	+	+	240-130	25	6.7	4	0.11		1.012	+	+
		12/1/20	++	++	++	190-115	25	6.25	2.5	0.10	75	1.017	+	+
		8/1/21	++	++	++	135-95	30.5	5.75	1.9	0.11		1.014	+	+
79 R	57	6/1/20	++	++	++	210-125	10	2.25	1.81	0.09		1.020	+	+
29 H	56	9/1/19	++	++	++	195-115	13.5		0.08	0.204		1.012	0.35%	++
		10/9/19	++	++	++	190-125						1.014	0.275%	++
		10/21/19	++	++	++		32.5		3.08			1.018	0.4%	++
85 H	50	7/3/20	++	++	++	140-95	17.5	4.1	2	0.11	77	1.024	++	++
		7/10/20	++	++	++	155-110	15	3.25	1.5	0.083	65	1.020	++	++
36 G	69	12/19/19	++	++	++	185-105						1.026	0.1%	++
		12/22/19	++	++	+		22		1.95	0.07		1.022	+	++
20 H	68	8/30/19	++	+	++	235-125						1.020	++	++
		8/31/19	++	+	++	180-115						1.022	++	++
		9/1/19	++	+	++	160-115	99		7.4	0.096		1.022	++	++
		8/8/19	++	+	++	215-110						1.022	++	++
14 W		8/9/19	++	+	++	195-105	11.5		1.6	0.14		1.025	+	+
22 T		8/29/19	++			190-125	19		2	0.10		1.022		
		9/1/19				210-125								



**CASE 1 (45)—History**—J F, aged 51, seen April 12 1921, complained of increasing dyspnea and recent orthopnea. He had been aware of some shortness of breath since a severe attack lasting several hours three years ago, when he ran up a long flight of stairs. For six weeks it had been more troublesome, so that he could only walk two blocks when he had to stop and rest and for three weeks he had been unable to lie flat in bed, requiring three or four pillows. He had no digestive symptoms, edema or cough. He had not given up his business, which was mostly sedentary.

**Examination**—Moderate cyanosis, dilated heart (left border 5 cm to the left, in the sixth space) with moderate systolic murmur at apex, transmitted to axilla, and a softer systolic murmur at the base was noted. There was moderate respiratory effort. Blood pressure, 210/135, pulse regular. Urine passed in the office showed excessive albumin, and many hyaline, fine and coarse granular and cellular casts, no blood.

The picture was that of a cardiac breakdown assumed to be secondary to hypertension of some duration. The urine suggested nephritis and further study.

**Treatment**—He was put to bed, given digitalis in sufficient dosage, and when seen two days later he was breathing easier and passing sufficient urine and there was but a trace of albumin. The chemical examination of the blood is shown in Table 4, revealing practically normal values. From this and the general picture, it was assumed that the kidneys, while in all probability the seat of interstitial change, were embarrassed from insufficient circulation (chronic passive congestion).

TABLE 4—RESULTS OF EXAMINATION OF BLOOD OF J F (CASE 1)

Date	Blood Pressure	Urea	Uric Acid	Creatinin	Sugar	Specific Gravity	Albumin	Casts
April 12	210/135					1.016	Excessive	Many
April 14	205/130	15	2.17	1.4	0.12	1.010	Trace	Few
May 20	190/135	14	2.62	1.17	0.11	1.010	Trace	Few
Dec 17	190/130	16	3.12	2	0.10	1.012	Excessive	Many

**Course**—The course of the disease seemed to bear this out for after six weeks of general supervision, he had less dyspnea, the heart borders were nearer normal, and he was able to walk eight blocks without distress. He had required frequent courses of digitalis for recurrent cardiac embarrassment. During these recurrences albumin increased.

In the next five months he was up, and spending some time at the seashore, but with slight unusual effort cardiac symptoms recurred, always attended with increase in the evidences of renal embarrassment, but controlled by rest and digitalis. At one time, the heart dilated to the anterior axillary line, the liver became enlarged and tender, and slight edema appeared at the ankles. December 18 he was again seen in decompensation, the left border of the heart being in the anterior axillary line, the apical murmur loud, and the liver swollen and undoubtedly pulsating. He was given digitalis to nausea, the pulse rate dropped to 40 per minute, and the pulse became bigeminal, improving gradually on withdrawal of the drug and without the use of atropin, polygrams showed heart block. The electrocardiograph was not available then. The urine was much decreased in amount, contained excessive albumin (35 gm per liter in twenty-four hours' urine), and there were numerous casts, indican was excessive, and urobilin moderate. He was definitely jaundiced, and the liver was four and one-half finger breadths below the costal margin.

The course was steadily downward from this time to February 4, when he was mentally confused and so drowsy that he fell asleep while being examined. There was marked cardiac dilatation with dyspnea and Cheyne-Stokes respiration, anasarca, enlarged liver. The urine had cleared up considerably, there being a moderate trace of albumin and a moderate number of casts of all kinds. He died two days later.

*Comment*—This is primarily a case of heart disease throughout the clinical course of nine months, with recurring nephritic symptoms, the latter cleared up with cardiac improvement. At no time until a few days before death did a suggestion of uremia (drowsiness, mental confusion) appear, these symptoms were assumed to be due to cerebral edema, since the urine output was sufficient and albumin and casts had decreased. The patient died of heart failure. There were never evidences of other cerebral insults.

Albuminuria in this case seemed directly associated with cardiac weakness, there were no evidences of retention in the blood. While albumin decreased on the second day after rest and digitalis had been instituted, the practically normal blood values gave a sense of security as to serious damage in the kidneys, and later observations bore this out.

CASE 2 (81)—*History*—C S, aged 58, a farmer, complained of shortness of breath for over a year, dating back to six years before when he overworked and was laid up with his heart for a month. The amount of twenty-four hour urine, he said, was about 1 quart. He was under a physician's care three months before, when after a few weeks in bed, he was so much better that

TABLE 5—RESULTS OF EXAMINATION OF THE BLOOD OF C S (CASE 2)

Date	Blood Pressure	Urea	Uric Acid	Creatinin	Sugar	Specific Gravity	Albumin	Casts
June 25	155/125					1.020	Excessive	Excessive
June 28	160/125	15	2.75	1.9	0.089	1.010	Trace	Few
Sept	180/140	12.5	1.25	2.2	0.083	1.018	Moderate	Moderate

he was able to take up light work on the farm. He had had increasing difficulty with breathing, and much swelling of the legs for two weeks.

*Examination*—Slightly cyanotic, considerable respiratory effort. The heart was 6.5 cm to the left of the midclavicular line in the sixth space, the sounds were distant, due to some emphysema, there were no murmurs, blood pressure 155/125. The arteries were considerably thickened. The legs were markedly edematous, the swelling extending to the abdomen, and there was some ascites. Urine (office specimen) showed excessive albumin, excessive hyaline, large and small granular and few cellular casts, no urobilin.

*Treatment*—He was put to bed, diet restricted, and given sufficient digitalis. He had much nausea and vomiting for three days. The urine on the fourth day showed specific gravity, 1.010, trace of albumin, no casts found. The heart was compensating well, and with very little distress, there was but a faint trace of albumin, and no casts. Blood pressure, 170/90, pulse, regular, heart borders, 3.5 cm to left of midclavicular line in fifth space.

*Course*—Two weeks later there was some return of dyspnea and edema, and, after ten days of rest and occasional use of digitalis, he was up and about and steadily improving. Two months later, he had a cerebral hemorrhage with paralysis in the right arm and face. Blood pressure was then 180/140. Urine showed moderate albumin, moderate granular, and few cellular casts. He died in coma two days later. Result of chemical examination of the blood is shown in Table 5.

*Comment*—Cardiac symptoms predominated until two days before death, when there was a cerebral hemorrhage. At first nephritic symp-

toms were prominent, but there was no particular blood retention and these symptoms improved with cardiac compensation

**CASE 3 (50) —History**—J C, aged 50, seen first March 26, 1920, complained of occipital headaches for two weeks, which awakened him in the early morning. Headaches formerly were occasional, but for the last few days had been constant and severe. For years he had been a hard worker in a responsible position as manager in a large paper mill.

**Examination**—Blood pressure was 225/150. The brachials were moderately thickened, the heart was moderately dilated, but there was no edema or cyanosis. The urine showed a definite trace of albumin, with few casts. There were some infected teeth.

**Treatment**—Two weeks later, on restricted diet and rest, his blood pressure was 180/120, and the urine showed a faint trace of albumin, the headaches were less, and he was generally better. June 11 blood chemistry showed urea, 10, creatinin, 2, uric acid, 2.92, sugar, 0.08. The urine showed definite trace of albumin, specific gravity, 1.018, and a few granular casts.

**Course**—August 13 he had sudden dimness of vision of left eye, which was due to edema of the retina. His blood pressure was then 250/150, and remained high in spite of bed rest, diaphoresis, catharsis, etc. September 7, he complained of more headache and was having some anginoid pain in the precordium. In the next six weeks he improved considerably, and left for New York on a business trip where he developed acute pulmonary edema. He was seen by Dr. Frank Meara. After a time he went to Boston, and was seen by Dr. Locke, because he was having shortness of breath, and some edema of the ankles.

His course was gradually downward from this time on, and he died in June, 1921, of cardiac decompensation.

**Comment**—The symptoms in this case of arterial hypertension were primarily cerebral, and later cardiac. During the period of cardiac embarrassment, there was an increase in albuminuria. At no time were nephritic symptoms predominant. The blood chemistry did not indicate retention.

**CASE 4 (71) —History**—G, aged 74, seen first June 12, 1920, complained of dizzy spells and weakness.

**Examination**—Some respiratory effort, marked arteriosclerosis. The left border of the heart was 4 cm. to left of the midclavicular line, in the sixth space, with showers of small rales at bases posteriorly. The urine showed 0.2 per cent albumin, with many fine granular and rare cellular casts. Blood pressure, 185/105.

**Course**—He made marked improvement on rest and digitalis, so that, within a month, the albumin decreased to a very faint trace. There were only a few fine granular casts. Blood chemistry, June 14: urea, 13.5, uric acid, 2.5, creatinin, 1.33, sugar, 0.083.

**CASE 5 (6) —History**—J, aged 59, seen first May 12, 1920, had slight dyspnea on effort, flatulence, some mental confusion and amnesia.

**Examination**—This revealed heart 2.5 cm. to left of midclavicular line, in fifth space, soft, blowing, systolic murmur at apex. No marked evidences of cardiac embarrassment. Arteriosclerosis moderate. Blood pressure, 240/125. May 12 blood showed urea, 11, creatinin, 1.16, sugar, 0.09. Urine showed a trace of albumin and a few granular and hyaline casts.

**Course**—At present, two years after first seen, he is up and about, showing progressive mental confusion.

CASE 6 (17) —*History*—Mrs K, seen first Aug 31, 1916, aged 65, had had several fainting attacks, especially while straining at stool

*Examination*—Blood pressure, 280/150 Cerebral symptoms predominated, and increased gradually The urine showed definite trace of albumin, and moderate casts, and the heart never gave any particular concern In August, 1919, she had a partial aphasia, mental dulness and amnesia Her blood pressure was then 225/138 Blood urea, 25.5, creatinin, 2 and sugar 0.142 The urine showed no increase in albumin and casts

*Course*—In January, 1920, she had lobular pneumonia when albumin and casts increased in the urine, and the heart became dilated Blood chemistry at this time showed uric acid, 2.37, creatinin, 1.17 The blood pressure was 240/135 Her heart gave no difficulty but she was more aphasic and amnesic Blood urea was then 30.5, uric acid, 5.75, creatinin, 1.9 and sugar 0.11 The alkali reserve was 70

The fundi, at no time, have shown hemorrhage

*Comment*—This patient has had predominating cerebral symptoms since 1914, is ambulatory, and has never, except during pneumonia, shown cardiac embarrassment or nephritic symptoms The condition has been attributed to cerebral arteriosclerosis rather than to chronic uremia

CASE 7 (21) —*History*—J L, was seen first April 19, 1914, aged 69, complaining of persistent headaches, and his physician had told him he had kidney trouble

*Examination*—He was then a sturdy appearing, well built man with ruddy face and a tendency to cyanosis His blood pressure was 205/130 Heart borders slightly increased, and some crepitant râles at the bases of both lungs Urine showed definite albumin, and many, fine, granular casts He was mentally alert and normal Peripheral arteries were moderately thickened

*Course*—Up to May, 1919, he was seen at intervals, and much improved, with albumin appearing in faint traces or absent At that time, he had an acute cardiac breakdown with much albumin and many casts, gradually improving during the summer In September, his blood urea was 27, creatinin 4 and sugar 10 To August, 1921, he gradually showed mental confusion, some amnesia, and general feebleness, though he was able to be up and about, and cardiac and nephritis symptoms were not prominent He then had another cardiac breakdown following obstinate constipation The blood showed high uric acid values in May and December, 1920, and August, 1921, and in September, 1919, creatinin was high (4 mg), but in August, 1921, it had dropped to 1.9 All this time his diet had been practically constant and restricted

*Comment*—This man has been seen more or less regularly for eight years His long continued hypertension has resulted in decreasing cardiac strength On several occasions of heart decompensation, albumin and casts have appeared, disappearing with improved circulation The kidneys have given no other cause of concern, though for nine months the urine has shown definite traces of albumin, and a few or moderate hyaline, granular or cellular casts

CASE 8 (29) —*History*—H, aged 51, was seen Sept 28, 1919 complaining of shortness of breath and swelling of legs, for two months Was passing less than a quart of urine daily Digestion was normal Recurring symptoms for one and one-half years

*Examination*—He showed moderate cyanosis and marked dyspnea, with heart dilated to anterior axillary line and regular, systolic murmur at apex. Blood pressure, 195/125. Urine specific gravity, 1.012, albumin, 0.35 per cent, many hyaline and granular casts, and few cellular casts. Blood urea, 13.5, creatinin, 0.08.

*Course*—Under treatment the symptoms improved somewhat, though the heart remained dilated, and albumin and casts persisted. The edema decreased. October 21 the blood urea was 32.5, creatinin, 3.03, and sugar 0.0204. Urine showed more albumin (0.4 per cent) and many hyaline, granular and cellular casts. He was then lost sight of, but died a few weeks later.

*Comment*—This patient's symptoms were predominatingly cardiac, with obstinate renal embarrassment. The high sugar content of the blood is noteworthy though glycosuria did not appear.

CASE 9 (85)—*History*—H, aged 50, was a typical "cardionephritic."

*Examination*—When admitted to the clinic his blood pressure was 195/120, orthopnea, slight edema, oliguria, and marked albuminuria were present, with heart dilated and decompensated. His course was steadily downward for six months, although for a time he improved under cardiac stimulation, rest and limited diet.

*Course*—July 3, six months after he was first seen, he again presented himself, with marked edema, cyanosis, dilated heart with auricular fibrillation. His blood at that time showed urea, 17.5, uric acid, 4.1, creatinin, 2, sugar, 0.11. The alkali reserve was 77. There was marked oliguria, excessive albumin and casts. July 10 urea was 15, uric acid 3.25, creatinin, 1.5, sugar, 0.083. Alkali reserve was 65. He died of heart failure a few weeks later.

CASE 10 (36)—*History*—G, aged 69, complained of dyspnea and orthopnea, considerable cough and flatulence.

*Examination*—Blood pressure, 185/105. Arteriosclerosis was marked, the heart was dilated 5 cm to the left of midclavicular line and showed auricular fibrillation. Urine contained albumin, 0.1 per cent. The blood showed urea, 22, creatinin, 1.95, sugar 0.07.

*Course*—In the next two weeks there was some improvement, but he died suddenly. Necropsy showed marked myocarditis.

CASE 11 (20)—*History*—H, aged 69, when first seen was semicomatose. For two months he had headaches on awaking, but for one week past was weak and had severe headaches, anorexia and vomited the day before.

*Examination*—Blood pressure, 225/125, urine much decreased and showing excessive albumin (0.35 per cent), many casts of all kinds.

*Course*—That night he had three convulsions on the left side of the body, but, when seen the next day, was not paralyzed. Blood pressure had fallen to 160/118 with pulse regular but weaker and the heart moderately dilated. The blood next day, showed extremely high values, as follows: Urea, 99, creatinin, 7.4, sugar, 0.96. He died that night.

*Comment*—This was evidently a case of hypertension of some duration seen near the termination of the disease when cerebral symptoms predominated. The high blood values showed serious retention. His heart, when first seen was fairly compensating. The clinical picture then suggested cerebral edema or uremia.

Another case of cerebral edema simulating uremia or "cardionephritis" is the following

TABLE 6—MISCELLANEOUS GROUP, SHOWING NORMAL BLOOD VALUES IN TWO CASES OF ORTHOSTATIC ALBUMINURIA, MARKED ALBUMINURIA IN CARDIAC DECOMPENSATION WHICH CLEARED UP WITH IMPROVED CIRCULATION THE VERY HIGH VALUES IN THE CASE OF BICHLORID POISONING HAVE BEEN NOTED BY OTHERS

Case	Age	Diagnosis	Urine			Edema	Uremia	Blood			Blood Chemistry				Test Diet Urine					Remarks
			Albu- min	Casts	Blood			Ol	Pres- sure	Urea	Uric Acid	Creat inin	Sugar	Alk.al Res	Pu	D	N	Gr	N	
67 S	28	Syphilitic nephritis	0.4%	+++	+	+	140/95	12.5	1.88	1.9	0.10		39	1,125	135	N	0.98	7.27	Nephritic symptoms disappeared after spe- cific treatment	
92 R	18	Orthostatic albuminuria	++	++			120/80	12.5	2.5	1	0.10	78	55	N	N	N			No symptoms *	
64 R	30	Orthostatic albuminuria	++	++			120/84	10	1.25	2	0.03		60	N	N	N			No symptoms	
M	23	Cardiac decompensation	0.6%	+++	+	+++	130/80							435	263	F ±	4.76	14	Symptoms disappear- ed with cardiac im- provement	
83 McD	28	Bichlorid poisoning			AN	+++	150/90	11.0	7.5	8	0.17								Anuria 48 hours, died	
41 S	12	Uremia	++++	+++	+	++	140/90	5.25	6.25	3.99			22						Duration 15 years, re- lapses with purpura	
23 C	45	Chronic parench nephritis	+++	+++	++	+++	190/120	4.25		2.5		11							Pus in tonsils, fever	
S	62	Acute focal nephritis	+	+	+	+	145/100							412	571	F ±	2.97	9.5		

**CASE 12—History**—Man aged 52, admitted to county hospital with some mental confusion and complaining of shortness of breath, cough and bloody sputum, was taken sick the day before. He had had heart trouble for about five months saying that he got it by trying to save someone from drowning. He had swelling of the ankles for four or five years. Difficult to get history because of mental confusion.

**Examination**—Much edema of the face and legs. The pupils were equal and reacted normally to light and accommodation. The heart area was increased, being about 2 cm outside the left nipple line. The heart was irregular in force and rhythm and there was pulse deficit. The first sound at the apex was replaced by a blowing murmur. On account of obesity the outline of the liver was not made out but there was also edema of the abdominal wall. Urine showed specific gravity, 1.014, albumin and hyaline and granular casts, two plus.

**Course**—He became comatose, had involuntary urination and defecation, and died in two days. Patient was shown before a class of medical students and discussed as a possible case of cerebral edema rather than one of uremia. Blood chemistry the day before death showed urea, 29, creatinin, 1.01.

**Necropsy Findings**—"Besides general edema there is an early gangrene of the toes of the right foot. The tips of the fingers are cyanotic and the hands are edematous. Two or three liters of amber colored fluid were found in the

TABLE 7—URINE FINDINGS IN CASE 13

Dry Urine	Albumin	Specific Gravity
On arising	0	1.028
11 a. m.	Def. trace	1.014
1 30 a. m.	Def. trace	1.024
4 p. m.	Def. trace	1.014
6 p. m.	Def. trace	1.018
8 p. m.	Def. trace	1.022
10 p. m. (retied)	Trace	1.024
11 30 p. m.	0	1.020

peritoneal cavity. The bowel wall is watery. The lungs are markedly emphysematous in front, both pleural cavities contain about a liter or more of straw colored fluid. The pericardial sac is distended with amber fluid. In the right auricle, especially in the anterior wall and in the appendix there is a large grayish organizing antemortem clot which is adherent to the wall. There are vegetations on the mitral valve. Sclerosis of the vessels and of the heart are not marked. There is a large infarct in the posterior portion in the upper lobe. The grayish antemortem embolus causing this infarct is found plugging one of the branches of the pulmonary arteries and there are multiple smaller infarcts. The whole lung is markedly edematous and congested. The left lung also shows several small hemorrhagic infarcts. The kidneys are of average size, the surtees made by sectioning disclosed an hyperemia but no other gross changes. There is a marked edema of the brain. The pia arachnoid is raised high above the convolutions. There is no scarring of the meninges. The vessels at the base of the brain are moderately sclerotic but there is no evidence of thrombosis or softening in any portion of the brain."

#### MISCELLANEOUS GROUP

**CASE 13 (92)—History**—R, aged 18, case of orthostatic albuminuria (Table 6) who had been refused admission to Annapolis on account of albuminuria. Never ill nor conscious that anything was wrong. Table 7 shows albumin present only in the day urine.

**Course**—The albuminuria was uninfluenced by diet and exercise, and repeated examinations showed no albumin in the urine passed on arising. The two hour

test diet was normal. The phenolsulphonephthalein output was 55 per cent in two hours. Blood chemistry showed urea, 12.5, uric acid, 2.5, creatinin, 1, sugar, 0.10. Alkali reserve, 78. This patient was later admitted to Annapolis.

CASE 14 (64) —*History*—R, aged 30, printer, case of orthostatic albuminuria, never knew he had albumin until he failed to pass the physical examination for the army. Repeated examinations of the urine showed trace of albumin and a few granular casts in spite of low protein diet, and not modified by exertion. Blood chemistry showed urea, 10, uric acid, 1.25, creatinin, 2, sugar, 0.8. Two hour test practically normal. Phenolsulphonephthalein output, 60 per cent. Albumin was present only when patient was upright. In neither case was there any evidence of polycythemia as noted by F. Eichenberger<sup>28</sup>.

These two cases of albuminuria showed normal blood values and the effect of posture on the albuminuria. Ludwig Jehle,<sup>29</sup> in 1913, showed the effect of lordosis and kinking of the ureter in producing this phenomenon. Barker and Smith<sup>30</sup> reported six cases, finding that, if the patient stood in an exaggerated lordotic position for one half hour, albumin and casts appeared in the urine. Sonne catheterized the ureters in his patients, and found typical orthostatic albuminuria in the left kidney only, giving the explanation that the vertebrae compress the renal vein. More recently W. and S. L. Rieser,<sup>31</sup> show that the aorta, or mesenteric artery, acts as pincers of the left renal vein. These become operative when the aorta is projected forward by lordosis, or when the mesenteric artery is pulled to tautness by visceroptotic tug from the mesocolon.

CASE 15 (83) —McD, bichlorid poisoning, seen in coma. Had passed no urine for forty-eight hours. Blood showed extremely high values as follows: urea, 110, uric acid, 8, creatinin, 7.5, sugar, 0.17. Died within a few hours.

CASE 16 (67) —S, aged 28, syphilitic nephritis, albumin, 4 per cent, many casts. Phenolsulphonephthalein, 39 per cent, blood showed urea, 12.5, uric acid, 1.88, creatinin, 1.9, sugar, 0.1. The test diet was given with the following results:

Time	Volume, C c	Specific Gravity	Cl	N
8-10	165	1.010	0.29	0.6
10-12	330	1.008	1.056	0.729
12-2	210	1.012	1	0.814
2-4	150	1.016	1.2	0.726
4-6	150	1.017	1.32	0.732
6-9	120	1.016	1.10	0.75
Total day	1,125		0.70	0.727
Total night	135			

The albuminuria disappeared on specific treatment.

CASE 17 (23) —C, aged 45, chronic parenchymatous nephritis, had had nephritis for eighteen years, with occasional relapses. Four years before had

28 Parkes Weber. Polycythemia, etc, New York, Paul Hoeber, 1922, p. 11.

29 An Explanation of Orthostatic Albuminuria, Editorial, J. A. M. A. **77** 127 (July 9) 1921.

30 Barker, L. F. and Smith, J. Functional Renal Tests in Orthostatic Albuminuria, Am. J. M. Sc. **141** 44, 1916.

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albuminuric retinitis Blood pressure varied between 210 and 110 In July, 1918, was seen with anuria for forty-eight hours, and profuse purpura on the arms and legs, and marked hematuria For six months she had been gradually failing, albuminuria had been excessive, there was marked edema, hydrothorax and ascites Blood chemistry showed urea, 42.5, uric acid, 2.5 sugar, 0.11 She was too sick to have a test diet, and died within a month

CASE 18—S, aged 62, acute focal nephritis This patient was seen during an attack of acute tonsillitis with fever Her blood pressure was 125/100 Heart negative Urine showed trace of albumin and few hyaline and granular casts but ten days later, there was oliguria, some edema of ankles and lower eyelids, and the urine showed a definite trace of albumin, hyaline and granular casts and red corpuscles There was no urinary calculus, and pyelitis and pyelonephrosis were ruled out The test diet was as follows

Time	Volume, Cc	Specific Gravity	NaCl	N
8-10	37	1.009		
10-12	75	1.014		
12-2	44	1.009		
2-4	61	1.014		
4-6	27	1.009		
6-8	168	1.005		
Total day	412		2.97	9.5
Total night 10/8	571			

Within a few weeks nephritic symptoms had all disappeared, and when seen three months later, she was entirely well

CASE 19—Mrs M, aged 23, cardiac decompensation, had been in bed for six weeks with cardiac decompensation Left border of the heart  $1\frac{1}{2}$  inches to the left of midclavicular line with mitral insufficiency and stenosis The liver was four finger breadths below the costal margin, and tender, marked edema of ankles, face, eyelids and buttocks Albumin, 0.6 per cent, many hyaline and granular casts The two hour test was as follows

Time	Volume, Cc	Specific Gravity	NaCl	N
8-10	39	1.012		
10-12	59	1.012		
12-2	79	1.012		
2-4	76	1.016		
4-6	87.5	1.008		
6-8	94	1.012		
Total day	345		4.76	14
Total night	263	1.011		

CASE 20 (41)—S, aged 12, nephritis with edema, had been in bed for some time before, with edema for last seven weeks Urea, 52.5 uric acid, 6.25, creatinin, 3.99, alkali reserve, 0.22 Patient died three weeks later

### CONCLUSIONS

1 Albuminuria as described may not be due to serious damage in the kidney and may even be excessive from extrarenal factors Passive congestion of the kidneys occurs not only in cardiac breakdown due to valvular insufficiency but may be a result of long continued heart strain from arterial hypertension

2 Albuminuria occurs so frequently as a part of the clinical picture of arterial hypertension that these cases form a large group in the

patients studied While chronic interstitial nephritis is assumed to be present, the "renal crisis" is often due to myocardial weakness and results in passive renal congestion

3 In a miscellaneous group, two cases of orthostatic or postural albuminuria are cited Renal function tests show no marked disturbance in the kidneys

4 But few cases of primary nephritis are recorded because not many were encountered

5 Of the various functional tests, those using the urine are disappointing The chemical examination of the blood seems to offer a means of early differentiation between renal or extrarenal albuminuria The test diet for fixation of specific gravity, and for the estimation of chlorid and nitrogen excretion and water output also gives an early clue of renal function

6 The term "cardionephritis" seems a misnomer in view of the fact that the nephritic symptoms may be largely due to congestion and not to extensive renal damage

7 Efforts to make clinical and pathologic nephritis conform still fail because of the complicated mechanism of renal secretion

8 Attention is called to the predominating symptoms in vascular hypertension Sooner or later every patient shows singly or jointly (a) nephritis (b) cardiac or (c) cerebral symptoms

## CLINICAL EXPERIENCE WITH QUINIDIN\*

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During the past year in this country and for some time previously abroad, there has been great interest in the restoration of normal mechanism by the action of quinidin sulphate in cases of auricular fibrillation. The present series of sixteen cases has been studied with special reference to the improvement in efficiency of the circulation following restoration of the normal rhythm, as judged by various subjective and objective criteria. Obviously, the fact that auricular fibrillation can be terminated is of little significance unless the health of the patient is thereby improved.

In general, the following routine of treatment was employed. The circulation was brought to the highest efficiency possible by rest, and in most cases by thorough digitalization. Two patients who had slow cardiac rates with no pulse deficit, cyanosis or edema, and whose only signs of cardiac insufficiency were dyspnea and limitation of activity, were not given digitalis. In the other cases, digitalis was stopped before the administration of quinidin. A small preliminary dose of quinidin sulphate was given to test for idiosyncrasy to the drug. No case of hypersensitivity was discovered. Then 20 gm was administered daily in five doses of 0.4 gm each at two hour intervals. This dosage was employed in order to maintain a high concentration in the body. It was continued until the cardiac mechanism became normal, or until unfavorable signs appeared, or until it became evident that the rhythm could not be changed. In one case 19 gm of the drug was given. No untoward effects except headache and an increase in the number of stools, were observed.

All observations on the mechanism were confirmed by electrocardiograms. The average systolic blood pressure during fibrillation was determined by the method of James and Hart<sup>1</sup>. The vital capacity is expressed in percentage of the normal calculated according to the formula of West<sup>2</sup>.

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\* From the Cardiographic Laboratory of the Johns Hopkins University and Hospital. Presented in abstract by title before the American Society for Clinical Investigation, Washington, D. C., May, 1922.

1 James, W. B., and Hart, T. S. *Am. J. M. Sc.* **147** 63, 1914.

2 West, H. F. *Clinical Studies on Respiration. Comparison of Various Standards for Normal Vital Capacity of Lungs.* *Arch. Int. Med.* **25** 306 (March) 1920.

## CASE REPORTS

**CASE 1—*Arteriosclerosis Auricular Fibrillation Myocardial Insufficiency***—Male, aged 49 No history of acute rheumatic fever or syphilis Scarlet fever at 12 Onset of cardiac symptoms four months before admission, with precordial pain and rapid development of palpitation, dyspnea and edema On admission signs of congestive heart failure cyanosis, orthopnea, edema Large heart, no sign of valvular disease Rhythm totally irregular Pulse deficit from 10 to 12 Peripheral arteriosclerosis Wassermann reaction negative The signs of congestive heart failure disappeared with rest and thorough digitalization, but the patient remained unable to leave his bed without rapid reappearance of symptoms of cardiac failure

**CASE 2—*Arteriosclerosis Hypertension Auricular Fibrillation Myocardial Insufficiency***—Female, aged 63 No satisfactory history of any acute infection Onset of cardiac symptoms three years before admission with palpitation, dizziness, and edema of ankles Symptoms slowly progressive with periods of relatively good health On admission obesity, edema of ankles and of lung bases Large heart No evidence of valvular damage Rhythm totally irregular Pulse deficit 4 Peripheral arteriosclerosis Wassermann reaction negative Moderate improvement with rest in bed and digitalis

**CASE 3—*Arteriosclerosis Emphysema Auricular Fibrillation Myocardial Insufficiency***—Male, aged 77 No definite history of any acute infection Patient noticed irregularity of pulse about three years before entrance Anorexia and nausea only symptoms of cardiac insufficiency On admission showed no dyspnea Marked cyanosis Slight edema of legs Numerous râles at lung bases Liver enlarged Large heart No sign of valvular disease Rhythm totally irregular No pulse deficit Peripheral arteriosclerosis Wassermann reaction negative No digitalis given

**CASE 4—*Rheumatic Heart Disease Mitral Disease with Stenosis Auricular Fibrillation Myocardial Insufficiency***—Female, aged 48 Acute rheumatic fever at 34 Slight dyspnea for ten years Nine months before entrance marked dyspnea and anorexia with great limitation of activity Pulse irregular at that time Digitalis for some time before admission without significant change On admission slight cyanosis, many râles at lung bases Heart large Diastolic murmur at apex Rhythm totally irregular Pulse deficit 26 Liver enlarged Wassermann reaction negative

**CASE 5—*Rheumatic Heart Disease Mitral Disease with Stenosis Auricular Fibrillation Myocardial Insufficiency***—Female, aged 38 Acute rheumatic fever at 8 Scarlet fever before 14 Onset of heart failure eighteen months before entrance, with dyspnea and nervousness Shortly before entrance developed palpitation, precordial pain, edema and excessive fatigue Digitalis did not relieve these symptoms On admission showed slight cyanosis and râles at right lung base Large heart Mid-diastolic murmur at apex Rhythm totally irregular Pulse deficit 12

**CASE 6—*Rheumatic Heart Disease Mitral Disease with Stenosis Auricular Fibrillation Myocardial Insufficiency***—Male, aged 58 Acute rheumatic fever at 43 Onset of cardiac symptoms two years before present entry with a transient attack of rapid irregular heart action, dyspnea, weakness and edema of ankles Hospital history at that time records irregularity with pulse deficit of from 17 to 24 Constant administration of digitalis was necessary to enable him to carry on light work On this admission slight cyanosis, slight dyspnea, no edema Large heart Apical systolic murmur, no diastolic heard (Subsequently, after the onset of normal mechanism, a rough presystolic murmur was evident) Rhythm totally irregular No pulse deficit Wassermann reaction negative

**CASE 7—*Exophthalmic Goiter Auricular Fibrillation Myocardial Insufficiency***—Male, aged 58 Scarlet fever and tonsillitis in youth Onset of symptoms of hyperthyroidism seven years before entrance Four operations on

thyroid Pulse totally irregular for one week following one of these For six years patient had dyspnea and palpitation For three weeks before entrance orthopnea and edema of ankles On admission he showed recurrent thyroid enlargement, marked exophthalmos and tremor Orthopnea Cyanosis Moderate general edema Heart large No sign of valvular disease Rhythm totally irregular Pulse deficit of 58 Wassermann reaction negative Rapid rate and large deficit persisted despite rest and digitalization

CASE 8—*Arteriosclerosis Emphysema Auricular Fibrillation Myocardial Insufficiency*—Male, aged 57 No satisfactory history of acute infections Onset of cardiac symptoms two years before admission with dyspnea Incapacitation for eight months On admission dyspnea, cyanosis, edema Emphysema Peripheral arteriosclerosis Large heart No evidence of valvular disease Rhythm totally irregular No pulse deficit Wassermann reaction negative Slight improvement after rest and digitalis

CASE 9—*Rheumatic Heart Disease Auricular Fibrillation Myocardial Insufficiency (Slight)*—Male, aged 29 Periapical abscesses, tonsillitis and tonsillectomy one year before entrance No acute rheumatic fever Excessive fatigue Slight dyspnea and indigestion for three years On admission no dyspnea, cyanosis or edema Heart slightly enlarged First sound roughened Rhythm totally irregular Wassermann reaction negative Digitalis not given About ten weeks after discharge with normal rhythm the patient began to have palpitation and excessive fatigue again His pulse was found to be totally irregular and he was readmitted in the same condition as on first entrance, for a second course of treatment

CASE 10—*Arteriosclerosis Emphysema Auricular Fibrillation Myocardial Insufficiency*—Female, aged 73 No satisfactory history of any acute infection Onset of cardiac symptoms one year before admission with dyspnea, cough, edema An electrocardiogram made four months before admission showed auricular fibrillation On admission emphysema Peripheral arteriosclerosis Heart large Systolic murmur at apex, diastolic at base Rhythm totally irregular No pulse deficit Wassermann reaction negative Rest and digitalis did not change the patient's condition

CASE 11—*Syphilis Emphysema Arteriosclerosis Auricular Fibrillation Myocardial Insufficiency Hydrocele*—Male, aged 58 Frequent tonsillitis in youth Onset of cardiac symptoms with dyspnea ten years before entrance Incapacitation for five years On admission cyanosis, dyspnea, orthopnea, edema, obesity Marked emphysema, heart large No evidence of valvular disease Rhythm totally irregular No pulse deficit Peripheral arteriosclerosis Liver enlarged Wassermann reaction positive Gross signs of congestive heart failure disappeared with rest and digitalis

CASE 12—*Rheumatic Heart Disease Mitral Disease with Stenosis Auricular Fibrillation Myocardial Insufficiency*—Male, aged 60 No history of any acute infection Symptoms of heart failure for fifteen years Palpitation, dyspnea, anorexia, vomiting, edema Two attacks of unconsciousness followed by aphasia On admission marked dyspnea, râles at lung bases, large liver Heart large Diastolic murmur at apex Rhythm totally irregular Marked peripheral arteriosclerosis Wassermann reaction negative Deficit of from 6 to 10 persisted despite digitalization with reduction of heart rate to 65

CASE 13—*Rheumatic Heart Disease Mitral Disease with Stenosis Auricular Fibrillation Myocardial Insufficiency*—Female, aged 54 Repeated tonsillitis in childhood Onset of cardiac symptoms five years before entrance, with palpitation and shortness of breath Three years before entrance rapid irregular heart action with increasing dyspnea Intermittent progression of symptoms On admission obesity, cyanosis, dyspnea Râles at lung bases Heart large No murmurs Rhythm totally irregular Pulse deficit 30 Wassermann reaction negative Moderate improvement followed rest and digitalis

CASE 14—*Rheumatic Heart Disease Mitral Disease with Stenosis Auricular Fibrillation Myocardial Insufficiency*—Female, aged 22 Repeated tonsillitis before 11 Admitted to hospital at 11 with tonsillitis, rheumatic heart disease, pericardial effusion, auricular fibrillation and signs of congestive heart failure The patient established a fair degree of cardiac reserve but was readmitted nine years later with marked failure, from which there was a good recovery The patient has constantly taken digitalis On admission she showed slight edema Large heart Diastolic apical murmur Totally irregular rhythm Pulse deficit 8 Wassermann reaction negative

CASE 15—*Rheumatic Heart Disease Mitral Disease with Stenosis Auricular Fibrillation Myocardial Insufficiency*—Male, aged 45 No history of acute rheumatic fever or syphilis Long history of ill health Onset of cardiac symptoms (dyspnea, vertigo, frothy sputum) one year before present entry Electrocardiogram at that time showed auricular fibrillation On admission dyspnea and cyanosis, no edema Large heart Middiastolic murmur at apex Rhythm totally irregular Pulse deficit 10 Wassermann reaction negative Constant administration of digitalis was necessary to prevent incapacitation Withdrawal of digitalis during administration of quinidin was followed promptly by serious congestive heart failure

CASE 16—*Rheumatic Heart Disease Mitral Disease with Stenosis Auricular Fibrillation Myocardial Insufficiency*—Male, aged 39 Repeated sore throat Onset of cardiac symptoms two years before admission with syncope, dyspnea, and gastro-intestinal symptoms Dyspnea grew slowly worse On admission dyspnea at rest and cyanosis Râles at lung bases Heart large Low pitched diastolic apical murmur Rhythm totally irregular No pulse deficit The patient was still bedridden after rest and digitalis

#### COMMENT

Table 1 summarizes the results of our observations Examination of this table shows that of sixteen patients studied, fourteen (88 per cent) responded to the administration of quinidin by reverting to the normal mechanism The average amount of the drug given to produce this result was 3.26 gm, the limits of variation being 0.4 gm and 10.0 gm This means that rhythm in most cases became regular on the second day of treatment, while the longest time which elapsed during successful treatment was five days Of the fourteen patients in whom rhythm became regular, normal rhythm has persisted in eight Six patients have had a normal rhythm for six months or more The eight patients in whom rhythm became persistently regular all showed a remarkable improvement, both subjective and objective, while none of the remaining six who soon reverted to auricular fibrillation showed improvement with the onset of normal mechanism This observation is of great interest because it points strongly to a close correlation between the severity of myocardial damage and the persistence of auricular fibrillation It is, however, noteworthy that there has been no close correlation between the degree of heart failure and the success of quinidin treatment

Conclusions as to the relation of the various etiologic factors, the duration of cardiac symptoms, and the age of the patient, to the success

TABLE 1—SUMMARY OF OBSERVATIONS

Case No	Etiologic Factor	Duration of Cardiac Symptoms	Degree of Cardiac Failure	Quinidin		Rhythm After Quinidin	Duration of Normal Rhythm†	Subjective Condition	Vital Capacity, per Cent of Normal		Systolic Blood Pressure	
				Days Given	Total Dosage, Gm				Auricular Fibrillation, per Cent	Normal Rhythm, per Cent	Auricular Fibrillation, Average	Normal Rhythm
1	Arteriosclerosis	5 months	Third	2	1.6	Auricular fibrillation	9 months	Much improved		85	110	110
2	Arteriosclerosis, hypertension	3 years	Second	3	5.6	Normal rhythm	3 days	Not changed	58	78	154	220
3	Arteriosclerosis	3 years	First	3	3.0	Normal rhythm	6 months	Improved			103	
4	Arteriosclerosis	3 years	First	4	6.4	Auricular flutter	6½ months	Much improved	52	68		111
5	Rheumatic infection	10 yrs (fibrillation 9 months) 18 months	Second	1	0.8	Normal rhythm	6 months	Distinctly improved	36	47	80	120
6	Rheumatic infection	18 months	Second	4	8.0	Auricular fibrillation	6 months	Greatly improved	50	87	92	120
7	Rheumatic infection	1 yr	First	3	6.0	Normal rhythm	6 months	Distinctly improved	67	92	95	105
8	Rheumatic infection	1 yr	First	½	0.8	Normal rhythm	6 months	Distinctly improved				
9	Rheumatic infection	6 yrs	Third	1	1.6	Normal rhythm	25 days	Greatly improved	50	83	88	130
10	Rheumatic infection	2 yrs	Third	1	2.0	Normal rhythm	3½ months	Greatly improved	48	63	100	110
11	Rheumatic infection	3 yrs	None	1	7.0	Normal rhythm	3 months	Distinctly improved				
12	Rheumatic infection	15 hrs	None	1	1.1	Normal rhythm	7 d	Not changed	110	126	93	120
13	Rheumatic infection	1 yr	Second	1	0.1	Normal rhythm	1 month	Not changed	126	128		
14	Rheumatic infection	1 yr	Second	1	1.6	Normal rhythm	2 months	Not changed	130	140	95	125
15	Rheumatic infection	1 yr	Second	1	1.0	Normal rhythm	2 days	Not changed			180	190
16	Rheumatic infection	2 yrs	Second	3	3.0	Normal rhythm	3 days	Not changed				
17	Rheumatic infection	2 yrs	Second	2	1.2	Normal rhythm	2 weeks	Not changed				
18	Rheumatic infection	9 days	Second	1	1.2	Normal rhythm	9 days	Improved	10	65	120	136
19	Rheumatic infection	2 days	Third	1	2.0	Auricular fibrillation	2 days	Not changed	40	35	100	145
20	Rheumatic infection	2 days	Third	2	2.8	Normal rhythm	3 days	Not changed				
21	Rheumatic infection	2 days	Third	1	1.6	Normal rhythm	2 days	Not changed				
22	Rheumatic infection	2 days	Third	2	2.8	Normal rhythm	24 hours	Not changed	48		120	
23	Rheumatic infection	24 hours	Second	3	6.0	Normal rhythm		Not changed				
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\* Cardiac failure is described in the following terms: first degree breathlessness on moderate exertion the chief symptom, second degree breathlessness on slight exertion, rales at lung bases, edema at the end of the day, moderate limitation of the patient's activities, third degree breathlessness at rest, gross edema, cyanosis, inappetence.

† Normal rhythm has persisted to the time of writing with the exception of Cases 9, 10, 13 and 14, the last three of which resulted in death.

of the treatment are not warranted in a series so small. Of great interest, however, is the success with which a very severe and long-standing case of thyrotoxicosis was treated.

With regard to the criteria of improvement, in addition to the subjective improvement which was experienced by all patients who became persistently regular, we have noted that they have been able to live at a considerably higher level of activity than was possible previously. Moreover, there has been consistently a rise in the vital capacity and systolic blood pressure of these patients. Determinations by Dr. Harold J. Stewart<sup>3</sup> of the degree of oxygen saturation of the arterial and venous blood further demonstrated a circulatory improvement in most of these patients.

Table 2 is a compilation of the cases of auricular fibrillation treated with quinidin which are reported in the literature, of which the total is now over 600. Normal rhythm was restored in more than 50 per cent of these patients. Reports of patients treated with quinin have not been included.

*Accidents*—There was a fatal outcome during the hospital course in three of the cases in this series. Unfortunately, two of these deaths seem to be associated with the change in rhythm which followed the administration of quinidin.

Shortly after reverting to normal mechanism for the second time, the patient reported as Case 13<sup>3a</sup> showed signs of renal insufficiency which were not previously present. Two days after the onset of normal mechanism she again relapsed to auricular fibrillation. The urine output fell almost to zero and examination of the blood showed increasing nitrogen retention. The patient had repeated convulsions and died five days after the onset of these symptoms. Necropsy revealed the presence of a friable thrombus in the left auricle. A large proportion of each kidney showed anemic infarction and surrounding hemorrhage. There was also infarction of the spleen and embolism of the abdominal aorta at its bifurcation. The brain showed a fresh clot over the right cerebral hemisphere. There was a moderate degree of mitral stenosis.

There was no change in the subjective condition of the patient reported as Case 14 after her pulse became regular. About twelve hours after the onset of normal mechanism she suddenly sat up and immediately thereafter fell out of bed and was found to be dead. No necropsy was permitted.

The patient reported as Case 11 was readmitted one month after her final assumption of normal rhythm. Three days previously symptoms suggestive of cerebral accident had suddenly occurred. Examina-

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3 Stewart, H. J. Arch Int Med (to be published)

3a This case is reported by the courtesy of Dr. Louis V. Hamman



TABLE 2—COMPILATION OF CASES OF AURICULAR FIBRILLATION  
REPORTED TREATED WITH QUINIDIN

Authors	Number Treated	Reversions to Normal Rhythm
Arnell <sup>4</sup>	9	4
Arrillaga, Waldrop and Guglielmetti <sup>5</sup>	14	9
Benjamin and von Kapff <sup>6</sup>	27	18
Boek <sup>7</sup>	35	16
Boden and Neukirch <sup>8</sup>	17	6
Burwell and Dieuaide	16	14
Clerc and Deschamps <sup>9</sup>	24	12
Drury and Hlescu <sup>10</sup>	13	6
Ellis and Clark Kennedy <sup>11</sup>	7	5
Fyster and Fahr <sup>12</sup>	2	1
Faber <sup>13</sup>	2	1
Frey <sup>14</sup>	50	21
Floystrup <sup>15</sup>	2	2
Haas <sup>16</sup>	44	27
Hamburger and Priest <sup>17</sup>	18	11
Hart <sup>18</sup>	15	5
Hewlett and Sweeney <sup>19</sup>	12	6
Jenny <sup>20</sup>	18	17
Klewitz <sup>21</sup>	13	1
Leschke and Ohm <sup>22</sup>	1	1
Levy <sup>23</sup>	25	11
Llin and Robin <sup>24</sup>	4	3
Oppenheimer, Mann and Felberbaum <sup>25</sup>	56	25
Romburg <sup>26</sup>	22	17
Sappington <sup>27</sup>	1	1
Schott <sup>28</sup>	2	2
Smith <sup>29</sup>	12	6
Van Tilburg <sup>30</sup>	10	8
Von Bergman <sup>31</sup>	9	6
White, Marvin and Viko <sup>32</sup>	75	51
Wilson and Herrmann <sup>33</sup>	1	1
Wiesser <sup>34</sup>	11	4
Wolferth <sup>35</sup>	12	7
Wybauw, Dumont and Joos <sup>36</sup>	27	14
Total	606	339 (55.9%)

- 4 Arnell P *Hygiea* **83** 529 1921  
 5 Arrillaga F C, Waldrop, C P, and Guglielmetti J *Prensa med Argentina*, **8**, 1922, (abstr in *Presse med* **30** 352 1922)  
 6 Benjamin and von Kapff W *Deutsch med Wchnsehr* **47** 10, 1921  
 7 Boek G *Med Klin* **17** 1052 1921  
 8 Boden, F, and Neukirch P *Deutsch Arch f klin Med* **136** 181 1921  
 9 Clerc A, and Deschamps N *Presse med* **30** 205, 1922  
 10 Drury, A N and Hlescu C O *Brit M J* **2** 511, 1921  
 11 Ellis, A W M, and Clark Kennedy A E *Lancet* **2** 894 1921  
 12 Fyster J A L and Fahr, G I *Arch Int Med* **29** 59, 1922  
 13 Faber, K *Ugeskr f Læger* **83** 577, 1921  
 14 Frey W *Deutsch Arch f klin Med* **136** 70 1921  
 15 Floystrup G *Ugeskr f Læger* **83** 1389, 1921  
 16 Haas H *Berl klin Wchnsehr* **78** 540, 1921  
 17 Hamburger W W and Priest W S *J A M A* **79** 187 (July 15) 1922  
 18 Hart T S *J A M A* **79** 69 (July 1) 1922  
 19 Hewlett A W, and Sweeney J P *J A M A* **77** 1793 (Dec 3) 1921  
 20 Jenny E *Schweiz med Wchnsehr* **51** 272, 1921  
 21 Klewitz, F *Deutsch med Wchnsehr* **46** 8 1920  
 22 Leschke F, and Ohm R *München med Wchnsehr* **68** 65 1921  
 23 Levy, R L *New York State J M* **22** 276, 1922  
 24 Llin O and Robin V *Bull et mém Soc med de hop de Par* **46** 23, 1922  
 25 Oppenheimer, B S, Mann H, and Felberbaum D *J A M A* **78** 1752 (June 3) 1922  
 26 Romburg L *Krankheiten des Herzens*, Ed 2 Munich, 1921  
 27 Sappington S W *J A M A* **78** 59 (Jun 7) 1922  
 28 Schott, E *Deutsch Arch f klin Med* **134** 208, 1920  
 29 Smith F M *J A M A* **78** 877 (March 25) 1922  
 30 Van Tilburg, J *Nederl Tijdschr v Geneesk* **2** 1553 1921  
 31 Von Bergman G *München med Wchnsehr* **66** 705 1919  
 32 White P D, Marvin H M and Viko L F *J A M A* **78** 1839 (June 10) 1922  
 33 Wilson F N, and Herrmann G R *J A M A* **78** 865 (March 25) 1922  
 34 Wiesser Inaug Dissertation Cologne, 1920  
 35 Wolferth C C *Am J M Sc* **162** 812 1921  
 36 Wybauw R, Dumont and Joos *Polechnique (Brussels)* March 1, 1921 (abstr in *Arch d mal du cœur* **14** 564 1921)

tion showed increased reflexes on the right side and a right facial weakness. The pulse was totally irregular, with short periods of regularity. An attempt was made to control the auricular fibrillation by the administration of quinidin (two doses of 0.2 gm each). This was ineffectual. The patient became comatose and shortly thereafter died. At necropsy it was found that there was a thrombus in the left middle cerebral artery and an infarction of the spleen. There was a moderate degree of stenosis of the mitral valve but there was no thrombus within the heart. There was extensive arteriosclerosis.

The frequent occurrence of embolism in cases of longstanding auricular fibrillation is well known. Mackenzie<sup>37</sup> and Orr<sup>38</sup> suggested that the contractions of the auricle, after quinidin had caused a resumption of its normal activity, might serve to detach emboli from intra-auricular clots. Table 3 shows that fourteen accidents resembling embolism have been reported as following closely the onset of normal rhythm in

TABLE 3—ACCIDENTS SUGGESTING EMBOLISM FOLLOWING THE ONSET OF NORMAL RHYTHM IN CASES TREATED WITH QUINIDIN

	Cases	Deaths
Benjamin and von Kapff <sup>8</sup>	1	1
Burwell and Dieuaide	2	2
Ellis and Clark-Kennedy <sup>11</sup>	2	2
Groedel <sup>39</sup>	1	1
Hewlett and Sweeney <sup>10</sup>	1	1
Levy <sup>23</sup>	2	1
Sappington <sup>27</sup>	1	1
White, Marvin and Viko <sup>32</sup>	3	2
Wilson and Herrmann <sup>33</sup>	1	0
Total	14	11

cases of auricular fibrillation treated with quinidin. Eleven of these accidents were fatal. Up to the present, however, no pathologic evidence as to the nature of these accidents has been available.

The necropsy findings in Case 13 leave no doubt that this patient's death was due to the mechanism suggested by Mackenzie and Orr. In Case 14 we can only speculate on the basis of the clinical course that the same mechanism was responsible for the patient's death. In Case 11 the hemiplegia occurred while the patient's pulse was totally irregular and, since there was no intra-auricular thrombus, it is felt that this fatality is not attributable to the use of quinidin.

The occurrence of such accidents in small series of cases brings out the fact that patients should be carefully studied before being given quinidin. It is, of course, impossible to decide whether or not there is present an intra-auricular thrombus. Therefore, the decision as to the

37 Mackenzie J. Brit M J 2 576 1921

38 Orr, J. Brit M J 2 576, 1921

39 Groedel, F. M. Therap d Gegenw 62 172 1921

use of the drug in a given case must be based upon a consideration of the degree of the patient's incapacitation after the usual therapy has been employed and of the improvement to be expected from a restoration of the normal rhythm. It must be borne in mind that embolism may occur during the course of auricular fibrillation and hence that the interpretation of embolic accidents following quinidin therapy must include a study of their relation to the onset of normal auricular activity. It is important to note that the drug is not in itself responsible for the embolism and that there is nothing to be gained by modification of the dosage.

#### CONCLUSIONS

Our observations of the patients' activity, systolic blood pressure, vital capacity, and subjective condition show a consistent improvement in all patients whose cardiac rhythm became regular and remained so for some time. Therefore, in patients with auricular fibrillation who cannot be brought to a satisfactory degree of circulatory efficiency by the usual therapeutic measures, an attempt to cause reversion to normal mechanism by quinidin is justified by the hope that the patient's health will be improved thereby. It is well established that the change in rhythm can be effected in at least 50 per cent of the cases.

Two grams of quinidin sulphate may be administered daily without the production of severe toxic symptoms, and such a dosage results in a higher percentage of successes than does a smaller dosage.

So far as is known at present, the danger associated with the use of this drug lies not in its direct effects but in embolism from an intra-auricular thrombus, following the onset of normal auricular activity.

#### SUMMARY

1 Of sixteen cases of auricular fibrillation treated with quinidin sulphate, fourteen (88 per cent) reverted to normal mechanism.

2 Regular rhythm has persisted in eight of these patients, in six for more than six months.

3 In the cases remaining persistently regular there has been marked improvement in the patient's health.

4 Death occurred in three patients, in one, shown to be due to embolism from an intra-auricular thrombus.

## MYCOTIC (BACTERIAL) ANEURYSMS OF INTRAVASCULAR ORIGIN \*

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PHILADELPHIA

With the development of modern methods of clinical diagnosis and pathologic study, it has become universally recognized that arterial aneurysms, in the great majority of cases, particularly aneurysms involving the arch of the aorta, are due to syphilis. Other etiologic factors of clinical importance, although ranking far below syphilis, are bacterial or so-called mycotic infections of arteries, trauma (most frequently in connection with war wounds) and arteriosclerosis. Extremely rare causes are congenital defects of vessels, adhesions pulling the artery wall outward (traction aneurysms), vascular tumors and chemical erosion, such as may occur in the walls of gastric ulcer or carcinomas. In horses, a parasitic worm, the *Strongylus armatus*, has caused aneurysms involving most commonly the mesenteric artery.

Bacterial infections may invade the vessel wall either from the outside or from within. Those coming from without are usually due to the extension of infection to the vessel walls from neighboring or contiguous inflammatory foci, attacking, first, the adventitia and then spreading inward, producing disintegration of tissue until the vessel is weakened enough to yield. These aneurysms are found most often in tuberculous cavities, the walls of abscesses or other areas of inflammation. Rarely, the aorta or pulmonary artery may be involved, in which case the infection usually comes from bronchial lymph nodes. According to present day views, the aneurysms in periarteritis nodosa are also to be regarded as due to infection from without. Klotz,<sup>1</sup> who has recently studied this condition and reviewed the literature, believes that the organisms concerned are streptococci. The infection is thought to be spread along the periarterial lymphatics.

The types of aneurysms to which we wish to call attention are those in whose production bacterial infection from within the vascular apparatus plays a part. Infection may be brought to arteries in a variety of ways and other factors beside infection may also be of importance in giving rise to aneurysm. There is no satisfactory name to include all the types and distinguish them from the aneurysms caused by infection from without. Embolism is frequently a factor, and aneurysms in whose formation embolism plays a part were called by

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1 Klotz J M Research 32 1, 1917

the older writers, before the importance of infection was understood, embolic aneurysms. It is better to reserve this name for aneurysms regarded as being due to embolism without infection, although we do not believe that in any of the cases reported as purely embolic aneurysms without infection the absence of infection has been clearly established.

The term "mycotic" was adopted by Osler<sup>2</sup> and Eppinger<sup>3</sup> to call attention to the importance of infection. Eppinger's designation "mycotic embolic" for the type of aneurysm described by him has persisted. Benda<sup>4</sup> suggested "metastatic mycotic" to include the cases in which bacteria are carried to the vessel wall through the blood stream but without the aid of emboli. The name proposed by Benda does not cover the aneurysms caused by direct implantation of infection on the aorta and pulmonary artery. We have, therefore, designated the entire group "mycotic aneurysms of intravascular origin" which, at least, has the merit of directing attention to the two features they have in common.

Tufnell<sup>5</sup> is usually credited with being the first to recognize the importance of embolism in the production of aneurysms, although Virchow,<sup>7</sup> in 1847, six years before Tufnell's publication, not only furnished the proof that embolism occurs but noted that at the seat of embolism sharply delimited destruction of the inner and middle arterial coats may be found. In two cases, he found arterial dilatation and sac formation at the site of embolism.

Tufnell believed that the aneurysms were caused by pressure behind the embolus and developed there. Ponfick,<sup>8</sup> however, in 1873, showed that they occurred at the site of the embolus. He believed that the mechanical effect of the embolus being pushed against the vessel wall by the blood pressure behind it, injured the vessel and thus gave rise to aneurysm. In some emboli he found sharp calcareous spicules. Where the emboli were soft, he explained the damage to the artery wall as being due to the constant pressure of the embolus against it, a mechanism which he considered analogous to decubital necrosis.

2 Osler. Brit M J 1 467 1885

3 Eppinger. Arch f klin Chir 35 1887

4 Benda. Lubarsch-Ostertag Ergebnisse 8 196, 1901

5 The term mycotic, although sanctioned by long usage in this connection, is not altogether without objection since a special group of infections have come to be called the mycoses. With the exception of one aneurysm of the pulmonary artery, regarded as due to the spread of actinomycosis to the vessel wall (Reiche. Quoted from Thorel, Lubarsch-Ostertag, Ergebnisse 14 666, 1910) there are, so far as we are aware, no reports of aneurysms caused by any of the special group of mycoses.

6 Tufnell. Dublin Quart J M Sc 15 371, 1853

7 Virchow. Virchows Arch f path Anat 1 272, 1847

8 Ponfick. Virchows Arch f path Anat 58 528, 1873, 67 384, 1876

Goodhart,<sup>9</sup> who reported a number of cases of so-called embolic aneurysms in 1877, was the first to advance the hypothesis that infectious processes were concerned in their formation. In 1878, Buchwald<sup>10</sup> found bacteria in polypoid vegetations in a pulmonary aneurysm, but believed the aneurysm came first and the vegetations and bacteria later. Osler,<sup>2</sup> in 1885, reported the finding of five aneurysms of the aorta in a patient with malignant endocarditis. He believed that the endocarditis and the aneurysms were due to the same infection. Langton and Bowlby<sup>11</sup> found numerous bacteria in the walls of embolic aneurysms and concluded that the infection was derived from the heart valves.

Eppinger,<sup>3</sup> whose classic monograph appeared in 1887, has contributed most to our knowledge of this subject. He described minutely the arterial changes in various stages of what he called mycotic embolic aneurysms, and demonstrated that the infection was conveyed by bacteria laden emboli detached from the heart valves to the arterial wall, and that the formation of aneurysm was dependent on partial disintegration of the wall, particularly the internal elastic lamina. Eppinger believed that the infection was carried to the adventitia and set up inflammation there first, later spreading to the media and intima. Later investigators accept this as the course of events when tiny infected emboli enter the vasa vasorum and are held in the adventitia, but it is now generally believed, through the work of Unger<sup>12</sup> and others, that when emboli plug the lumen of an artery, inflammatory processes begin on the inner surface and spread outward.

Although Eppinger and others who followed him established the etiologic importance of infection in the formation of aneurysms, the view was not abandoned that the mechanical effect of embolus alone on an artery wall is able to cause aneurysm. Lecky,<sup>13</sup> Libman<sup>14</sup> and Reiche<sup>15</sup> within the past twenty years have reported cases which have been cited in support of this view. In Libman's case, bacteria were found in the heart valves, and in Reiche's case, while blood cultures were negative at the time the aneurysm developed, they had previously been positive. In Lecky's case, a purely embolic etiology for the aneurysm is strongly suggested, but the case report is too incomplete for the acceptance of this view without question.

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9 Goodhart Tr Path Soc Lond **28** 107, 1877

10 Buchwald Deutsch med Wchnschr **4** Nos 1, 2 and 3, 1878

11 Langton and Bowlby Med-Chir Tr **70** 117, 1887

12 Unger Beitr z path Anat u z allg Path **51** 137, 1911

13 Lecky Brit M J **2** 1127, 1906

14 Libman Proc New York Path Soc, N S **5-6** 88, 1905-1906

15 Reiche Quoted from Libman, Am J M Sc **144** 313, 1912

The more recent literature has shown that in the great majority of acute and subacute aneurysms developed from within the vessels, the underlying infection is some form of bacterial endocarditis. In this group of infections, aneurysms not only of the arteries but also of the heart walls and valves are not uncommon. Horder,<sup>16</sup> in 150 cases, found twelve aneurysms of the valves, four of the ventricular wall, four of the interventricular septum and four arterial aneurysms. In the series of Schottmuller,<sup>17</sup> Lenhartz<sup>18</sup> and Billings,<sup>19</sup> forty-four cases in all, six were found to have arterial aneurysms. Libman<sup>20</sup> has reported a total of thirteen mycotic aneurysms in three cases during the active stage of bacterial endocarditis. Cotton mentions the finding of but one aneurysm in a series of fifty-five cases of bacterial endocarditis. Morawitz<sup>21</sup> goes so far as to state that the development of aneurysms in unusual situations may aid in the diagnosis of "endocarditis lenta."

The older writers frequently attributed these aneurysms to rheumatism. Koch<sup>22</sup> in 1851, was the first to report such a case. From the published data in his case, as well as in many cases reported later, it seems more likely that bacterial endocarditis was present rather than rheumatism. More recently, rheumatism has not so often been regarded as of direct etiologic importance. In view of the difficulty in some cases, even at the present time, of making a differential diagnosis between the two conditions, it is not surprising that some confusion should occur. The importance of rheumatism as an etiologic factor in aneurysm formation will be discussed later.

The development of aneurysms during the course of bacteremia without endocarditis is rare. Buhl,<sup>23</sup> in 1866, found dissecting aneurysms of the ductus botalli in infants with puerperal infection. He concluded that the destructive processes must have been brought through the blood stream. Scattered reports of aneurysm formation in various conditions, principally bone and lung infections, are found, but until Ruge's<sup>24</sup> report, in 1905, none had had adequate bacteriologic study. Ruge's patient had osteomyelitis, pyemia and a coronary artery aneurysm in which streptococci were found. Since that time several cases have been studied bacteriologically, and streptococci,

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16 Horder. *Quart J M* 2 289, 1908

17 Schottmuller. *Munchen med Wchnschr* 57 617 1910

18 Lenhartz. *Nothnagel's specielle Pathologie und Therapie* 3 380, 1904

19 Billings. *Arch Int Med* 4 409 (Sept) 1909

20 Libman. *Proc New York Path Soc*, N S 5-6 43, 1905-1906

21 Morawitz. *Munchen med Wchnschr* 68 1478, 1921

22 Koch. *Inaugural-Dissertation* Erlangen, 1851

23 Buhl. Quoted from Thoma. *Deutsch med Wchnschr* 15 309 1889

24 Ruge. *Deutsch Ztschr f Chir* 80 150 1905

pneumococci or staphylococci were recovered from the aneurysms. The aorta and the hepatic artery are the vessels that have been involved most often.

#### REPORT OF CASES

##### MYCOTIC ANEURYSMS OF THE AORTA

**CASE 1—History**—A C., housewife, aged 31, white, American, was admitted to the University Hospital May 20, 1920, complaining of weakness and shortness of breath. Ever since she could remember, she had had palpitation and breathlessness on exertion, and during her childhood, a physician stated that she had a weak heart. In September, 1919, she began to suffer from chills, fever, cough and weakness. In October, her joints began to swell and were slightly painful. By February, 1920, she was somewhat improved but then developed what was called influenza. She had anorexia, sore eyes, headache, cough and pains all over her body, sensations of chilliness and marked weakness. Soon her feet and legs began to swell and she became so short of breath that she could not lie down flat. There was also some cough with white frothy expectoration.

She had never had any joint affections except the mild attack in the beginning of her present illness and had never had chorea. She had had measles and chickenpox in childhood, at 6 years she had some illness the nature of which was not known, but there was swelling of the body and redness of the skin. She had typhoid fever at 16.

Her habits had been good, she lived in good surroundings and she had done her housework. Her husband and two children are living and well.

**Physical Examination**—She was of about medium stature, with poor nutrition and musculature. The skin was pale but there were no eruptions, except some miliaria on the chest and abdomen. The breathing was accelerated, shallow and somewhat labored. The lips and oral mucous membranes were pale, the teeth unclean, there were many cavities and unextracted roots and the gums were retracted. The tongue was heavily coated. The chest showed poor expansion, somewhat less on the left side. There were signs of congestion and some fluid at both bases. The cardiac apex impulse was weak and diffuse. The percussion area of precordial dullness was enormously increased, extending 13 cm. to the left of the midsternal line and 11 cm. to the right. The substernal dullness was 8 cm. in the first interspace, 12 cm. in the second and 17 cm. in the third. There were vigorous visible and palpable pulsations in the second and third interspaces to the right of the sternum. Loud systolic and diastolic murmurs were heard over the aortic area, probably also a separate apical systolic murmur. There was an occasional extrasystole. The liver was markedly enlarged and there were signs of a small amount of fluid in the abdomen. The spleen could not be palpated. There was moderate edema of the back but none of the legs. There was marked clubbing of the fingers. The pulsations in the larger arteries were visible, a distinct capillary pulse was seen and the Traube and Durosiez signs were present. The blood pressure was 100 systolic. Eyeground examination showed only pulsation of the retinal vessels.

**Laboratory Examination**—The examinations of the urine showed a specific gravity of from 1.012 to 1.014, persistent cloud of albumin, many hyaline and granular casts, a slight excess of leukocytes and a few erythrocytes. The hemoglobin was 40 per cent, the erythrocyte count 2,230,000, and the leukocyte count 11,300 with 75 per cent of polymorphonuclears. The Wassermann test was negative. A blood culture was positive, showing *Streptococcus viridans*.

The report of the roentgen ray of the chest by Dr. H. K. Pancoast was as follows: "Large heart. Right side of shadow less dense suggesting fluid on the right side. May be fluid in the pericardial sac."



The temperature was of an irregular septic type, ranging from 97.4 to 103.6 F. Pericardial frictions developed and were heard over a wide area. There was manifest very little change in her general condition until June 5 when the pulse became very rapid and weak and the breathing labored. In a short time, death occurred.

*Diagnosis*—*Streptococcus viridans* endocarditis, aortic and mitral regurgitation, myocarditis, pericarditis, cardiac decompensation with passive congestion of the lungs, liver and kidneys, mycotic aneurysm of the ascending arch of the aorta, subacute nephritis, secondary anemia.

*Comment*—In spite of the fact that the literature affords no instances of a clinical diagnosis of mycotic aneurysm of the arch of the aorta confirmed at necropsy, the diagnosis in this case was based on the extraordinary degree and extent of visible and palpable pulsation to the right of the sternum in the second and third interspaces, associated with clear evidences of an aortic valve lesion, fever, leukocytosis and other evidences of an active infectious process. The discovery of pulsation over the arch of the aorta to the right of the sternum is to be expected in some cases of aortic regurgitation and is explained by the dilatation of the root of the aorta which occurs to a greater or less extent in many cases of this condition. The violence and the extent of the pulsation in this case were, however, so marked, and the evidence of unusual dilatation of the arch of the aorta on percussion so definite, that it seemed altogether probable that a distinctly pathologic dilatation (as contrasted with mere overdilatation from stretching) existed in this case. The evident intravascular infection furnished a probable explanation, as acute (mycotic) aneurysmal dilatations are known to occur in association with infective endocarditis.

*Pathologic Examination*—The necropsy was performed by Dr. M. T. McCutcheon. The following notes have been abstracted from his report:

The heart weighed 770 gm., the epicardium was reddened and covered with fibrin which was easily stripped off in some places and adherent in others. The muscle was flaccid and of a turbid flesh color. The left side of the heart was greatly dilated, the right less so. The mural endocardium was generally transparent, but on the wall of the left ventricle below the aortic valve and on the left auricle above the mitral valve were found numerous soft verrucae. Two aortic leaflets show thickening, the right posterior one was much eroded and from it hung a soft vegetation about 8 mm. in length. The mitral valve was unthickened, but covered with many verrucae, some of which were quite pale and firm, while others appeared fresh. Smears made from the aorta just above the aortic valves and stained for bacteria showed streptococci.

In Figure 1 are shown an aneurysm and ulcerations in the ascending arch of the aorta and their relations to the aortic valve. Just above the right posterior sinus of Valsalva are two ragged ulcerated areas. On the corresponding aortic leaflet, there are two long but soft vegetations the tips of which could be inserted into the ulcerations. There are also some small vegetations about the ulcerations. In this area, about 2 cm. wide and 1 cm. long, the aortic wall is slightly thickened and pouched out. To the right, the diseased area narrows to an isthmus of thickened and slightly depressed vessel wall which connects it with a definite aneurysm above the anterior sinus of Valsalva. The aneurysm is irregularly rounded, approximately 2 cm. in diameter, and in the hardened specimen the floor is about 1.25 cm. below the surface of the adjacent part of the vessel. It extends just low enough to include and hide the exit of the right coronary artery. By probing back

through the artery, the exit was found not to be blocked but it was surrounded by fine vegetations. The wall of the aneurysm in places was from two to three times the thickness of the nearby vessel wall and was quite firm. There were folds in it suggesting that it had been larger during life and had contracted postmortem. For the most part it was covered by a smooth lining continuous with the intima and resembling it somewhat, although it was not quite so glistening and delicate. A few ragged vegetations were found growing out from this layer and on the left border of the aneurysm there was a ragged irregular area of ulceration about 6 mm in diameter. At the edges



Fig 1—Case 1. Drawing of wall of left ventricle, aortic valves and the aorta just above the valves. There are two long ragged vegetations on the right posterior aortic leaflet. Above each on the inner surface of the aorta is an ulceration (*u*) to which the free end of the corresponding vegetation extends. The aneurysm (*a*) is above the anterior leaflet. The mouth of the right coronary artery at the lower end of the aneurysm is concealed but the vessel is patulous.

of the aneurysm the transition to healthy appearing aortic wall was abrupt. The rest of the aorta grossly appeared quite normal, except for one small subintimal yellow area 25 cm above and to the left of the aneurysm.

A section taken at the edge of the aneurysm running from the normal aortic wall into the ulcerated infiltrated area showed the following. Where

the vessel wall is grossly unchanged the intimal surface is largely missing, but what is present seems thickened. The internal elastic lamina is fairly solid. The media is irregularly degenerated, the muscle fibers in places being replaced by deep eosin staining spots and strands, at which places the elastica is also absent. Deep in the media, round cells begin to increase. The adventitia is very wide and consists of highly vascular, irregularly placed, strands of poorly stained connective tissue with a little muscle. Many of the vessels have a mantle of round cells. Some show distinct intimal swelling and one obliterated vessel is seen. There are a few round cell groups aside from the perivascular ones. The transition from the better preserved aorta to the aneurysmal part is indicated by a loose fibrous tissue participated in by the intima and media. Elastic tissue of the former practically disappears or becomes granular only, and of the latter is only fragmentary. The adventitia at this point is similar to that in the area previously described but somewhat more cellular, the elements being lymphoid and plasma cells. A few polymorphonuclear cells were seen. The blood vessels have distinctly more cellular walls. At the aneurysmal end of the section is an atheromatous abscess around the walls of which are polymorphonuclear cells, a few swollen cells of the endothelial type, some with phagocytic properties, and detritus. No bacteria were found in the sections stained for that purpose.

*Comment*—It is apparent from the pathologic examination of the aneurysm that the inflammatory process involving the aorta must have been present for some time a matter of at least months. In places the inflammatory reaction had almost completely subsided and the normal structure of the artery had been replaced by fibrous tissue. On account of the duration of the condition, the pathogenesis of the aneurysm is obscured. One of two modes of infection of the arterial wall seems probable. The infection may have been directly transferred to the inner surface of the aorta from the large ragged vegetations on the aortic valves which must constantly have come in contact with it. This view is favored by the finding of two acutely ulcerated areas in the aorta corresponding to the position in which the tips of two long vegetations would likely be thrown at each systole of the ventricle. On the other hand a mycotic embolic infection through a coronary twig supplying the aorta cannot be excluded, and in view of the close proximity of the infective material to the exit of the coronary arteries, has just as much to support it as infection of the artery by contiguity.

*CASE 2—History*—J. B., negro, male, aged 49, was admitted to the University Hospital, Nov. 4, 1921, complaining of aches and pains all over his body. He stated that about two years before admission he began to suffer from attacks of dizziness, and a year later he began to feel constantly tired and drowsy and had pains in his neck, chest, back and left leg. These symptoms persisted, and in addition, about six months ago, he noticed dyspnea on exertion. Four months ago, he had to give up work. Recently he thinks he "caught cold" and feels much worse since then. He has lost about 30 pounds.

He had gonorrhea at 18, and two severe and several mild attacks of rheumatism the first attack at 20. Three years ago he had a hard pimple on the penis which disappeared in five days. He is a restaurant waiter and his meals are irregular. He has not used tobacco or alcohol excessively. He is married his wife is living and well and has had one healthy child but no miscarriages.

*Physical Examination*—He was a well nourished negro who did not appear as old as his stated age of 49. The oral mucous membrane was pale, the breath fetid and the tongue coated. There was moderate pyorrhea and several broken tooth crowns. The tonsils were large, congested and cryptic. The chest was somewhat barrel-shaped but the lungs were clear throughout. The heart was enlarged, principally to the left. By percussion, the left base was 13 cm and the right base 4 cm from the sternal line. The supracardiac dullness measured 6 cm in the first interspace and 8 cm in the second. The apex impulse was diffuse and its outer border was in the fifth interspace just outside the midclavicular line. No pulsations over the base were noted. There were no thrills. There were systolic and diastolic murmurs over the aortic area. An occasional extrasystole was heard. The pulse was of the collapsing type. Traube and Durosiez signs and a capillary pulse were present. The blood pressure was 125 systolic. Examination of the abdomen was negative and neither spleen nor liver were palpable. The left knee was tender and swollen from effusion about the joint. Motion caused some pain.

After his admission to the hospital, the patient became more comfortable and in a few days the effusion in the knee subsided but did not disappear altogether. The temperature was irregular, varying between 97 and 103 F, and did not fall with the improvement in the knee joint. The pulse range was from 90 to 120.

*Laboratory Examination*—The urine examinations showed traces of albumin, hyaline, light and dark granular casts, a slight excess of leukocytes and on some examinations a few erythrocytes. The first blood count showed 3,600,000 erythrocytes, 5,600 leukocytes and 66 per cent hemoglobin. The differential count was normal. The Wassermann test was negative. Two blood cultures were positive for a short chain nonhemolytic streptococcus. The phenol-sulphonephthalein excretion was 40 per cent in two hours, and the blood urea nitrogen was 19 mg per 100 cc.

*Diagnosis*—A diagnosis of subacute infective (streptococcic) endocarditis was made.

*Course*—November 16, there developed within the course of a few hours, complete left sided hemiplegia. The next day there were symptoms of meningitis, and a spinal puncture was done. The fluid was under great pressure and slightly cloudy. There were a great many leukocytes in the fluid and a streptococcus was grown resembling the one found in the blood culture. After a few days, the meningeal symptoms disappeared, but the hemiplegia remained. These phenomena were regarded as due to the lodgment in the brain of a septic embolus from the heart.

Symptoms of cardiac failure and passive congestion developed gradually and death occurred Jan 4, 1922.

*Necropsy Report*—The necropsy was performed by Dr Baldwin Lucke to whom we are indebted for the pathologic report and the photographs of specimens.

*Gross Anatomic Diagnosis* Aorta Arteriosclerosis, early mycotic aneurysm. Heart Hypertrophy, cloudy swelling, acute ulcerative and vegetative aortic and mitral endocarditis, slight coronary sclerosis. Lungs Chronic passive congestion with superimposed edema and terminal congestion. Spleen Septic infarction, acute diffuse splenitis. Kidneys Chronic tubular nephritis, slight arteriosclerosis, infarction, slight hydronephrosis of left kidney.

*Detailed Inspection of Heart and Aorta* The heart is greatly enlarged, somewhat globular in shape, and measures 14 by 12.5 cm, weight, 550 gm. The epicardium is smooth and glistening and contains a normal amount of fat. The muscle is very dull, turbid and grayish brown. The left ventricular wall averages 20 mm and the right 3 mm in thickness. The papillary muscles are normal. The aortic leaflets are the seat of large soft vegetations, the right posterior cusp is almost entirely destroyed, the other two cusps possess

eroded margins. The mitral leaflets at their bases and midway between the base and the edge are covered with a few soft vegetations, the largest being about the size of a pea. The vegetations also extend down the chordae tendineae. The pulmonary and tricuspid valves have normal leaflets. The coronary arteries are slightly sclerotic. The aorta has normal calibre but much diminished elasticity. There are numerous, slightly elevated, hyaline and atheromatous patches, but nowhere any puckering. The aortic branches are slightly stiffened and have a slightly corrugated intimal surface. About 1 cm above the left posterior cusp there is an ulceration of the aorta. This has an oval shape and measures 15 by 10 mm. The margins are fairly smooth. The erosion affects the intima and the greater part of the media. The bed of the ulceration consists of somewhat uneven fibrous tissue, probably adventitia. No definite bulging has as yet occurred, at the most there is slight cupping.

**Section Through Vegetation from Heart Valve.** The vegetation is papilloma-like, consisting of almost homogeneous eosin staining blood material in which are everywhere sprinkled irregularly deep blue staining bacterial colonies (cocci).



Fig 2—Case 2. The aneurysm (a), the surface of which measures 15 by 10 mm, is seen about 1 cm above the left posterior leaflet.

**Section Through Aneurysm of Aorta.** There is an abrupt oval out-pouching, the walls of which consist of very much altered aortic tissue. On either side of the out-pouching, the aorta possesses a fairly normal intima with only here and there a slight hyaline thickening, the hyaline substance is sometimes broken up and contains large cells with fat droplets. The media is unchanged, except that around some of the vasa vasorum there are mantles of small round cells, groups of similar cells are scattered through out both media and adventitia, being particularly prominent in the latter. In addition, a few larger vessels in the adventitia possess irregularly thickened walls with hyaline plaques in the intima. At the edges of the out-pouching, the muscular and elastic fibers are suddenly curved outward and soon lost. At the base of the out-pouching there are small areas where much distorted remnants of elastic and muscular fibers can still be recognized. Generally, the wall of the dilatation consists of a much thinned out adventitia, which is composed of loosely arranged

fibrous tissue, between which are scattered groups of small round cells and occasional larger pigment containing phagocytes. The media is only represented by the traces of muscular and elastic fibers mentioned. There is an inner layer of newly formed tissue thrown into irregular folds and projections, it consists of very young connective tissue, the cells of which are stellate and embedded in a mucinoid ground substance. Internally, an endothelial lining covers this newly formed tissue, and is continuous with the endothelial lining of the more normal aorta. Bacterial stains failed to bring out any bacteria, stains for spirochetes were likewise unsuccessful.

*Comment*—The aneurysm found in this patient's aorta was so small (Fig 2) that clinical evidences of its presence could not be expected and none were discovered.

There were several unusual features of interest from the pathologist's viewpoint. In none of the cases previously reported has complete or virtually complete healing of an aortic mycotic aneurysm been observed. A number of cases have shown healing in part of the

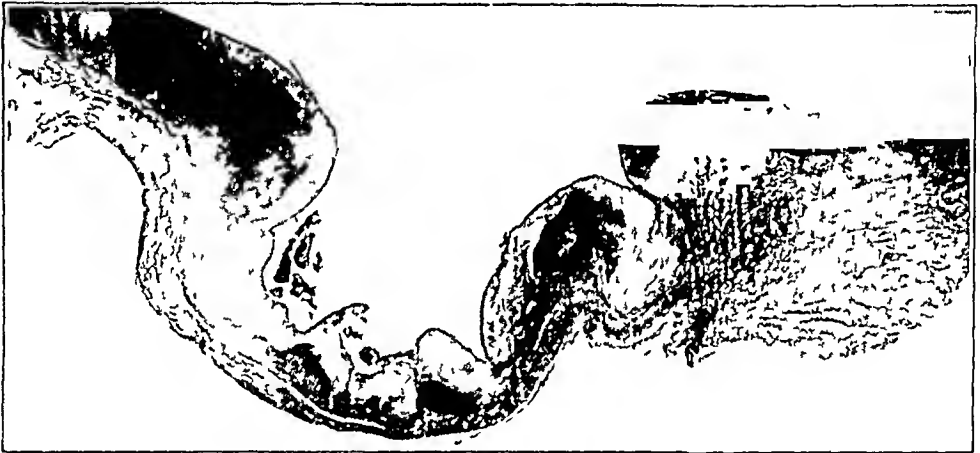


Fig 3—Case 2. Low power magnification, photomicrograph of section of the entire length of the aneurysm, stained for elastic tissue. At the edges of the aneurysm the elastic fibers are suddenly curved outward and soon lost. At the base of the out-pouching small remnants of elastic and muscular fibers can still be recognized.

aneurysm, but at the same time, active inflammatory processes were going on in other parts. According to Dr Lucke, the floor of the aneurysm in this case had been entirely covered over by a new growth of endothelium continuous with the endothelium lining the adjacent healthy portion of the vessel. No foci of acute inflammation were found anywhere. The destructive processes involving the media and the intima were of the usual type. These two tunics had been destroyed practically completely and were replaced by the layer of young connective tissue and endothelium previously mentioned. As shown in Figure 3, the wall of the aneurysm was much thinner than that of the normal part of the aorta.

On account of the chronicity of the aneurysm (Dr Lucke estimated its age at six weeks at the very least), and the fact that the inflammatory processes had subsided, there was not much evidence on which to determine the route by which infection had been brought to the artery. Infection by continuity from the aortic valve could be excluded as the vessel between the aortic valve and the aneurysm was not involved. There is little likelihood that the infection had been implanted directly from the valve on the aorta as there were no vegetations present at the time of necropsy anywhere nearly long enough to have reached the area of the aneurysm. It would seem most probable that a minute embolus had entered the coronary circulation from the diseased aortic valve and become blocked in one of vasa vasorum supplying the first portion of the aorta, initiating an inflammation that resulted in a true mycotic embolic aneurysm. Another possibility, although less likely, is that the process started as a metastatic infection of the inner surface of the aorta.

#### MYCOTIC ANEURYSMS IN BRANCHES OF THE SYSTEMIC ARTERIAL TREE

Two cases that fall in this group, both of which were somewhat unusual have been observed recently in the University Hospital.

**CASE 3—History**—A W, male, white, unmarried, aged 44, was admitted to the University Hospital, Sept 19, 1917. About three months previous to admission, he had begun to have chills, fever and sweats which recurred at irregular intervals. In August a tooth was extracted for root abscess and pus evacuated. Since then there had been no more chills and the temperature, which had previously gone as high as 104.3 F, no longer exceeded 101 F.

**Physical Examination**—The heart was found moderately enlarged, and there were blowing systolic murmurs at the apex and base. There were some râles at the right base posteriorly. The liver was enlarged and extended 6 cm. below the costal margin. The spleen was easily palpated on deep inspiration. There was slight tenderness along the course of the left femoral artery extending from Poupart's ligament halfway down the thigh. Small purpuric spots were noted in the skin. The blood pressure was 145/95.

**Laboratory Examination**—The blood examinations showed a slight secondary type of anemia with from 4,100,000 to 4,220,000 erythrocytes and from 77 to 82 per cent hemoglobin. The leukocyte count varied between 8,200 with 71 per cent of polymorphonuclear cells, and 16,800 with 84 per cent of polymorphonuclears. The urine showed small amounts of albumin and occasional casts and red cells. A blood culture remained sterile. Two examinations of the blood for malaria were negative.

**Course**—There was no change noted in his condition until September 29, when he complained of severe pain in the left groin. Slight swelling was noted in this area along the course of the femoral vessels. Moderate but irregular temperature, varying between 97 and 100.8 F, and a pulse range between 95 and 115 continued as before. The pain was very severe for a few days and then improved but persisted in lesser severity for a month or more. October 20, a distinctly localized tumor about the size of a walnut and with expansile pulsation was noted just below the left Poupart's ligament in the region that had previously been tender and swollen. The mass remained about the same size for a week or two but then began to grow smaller and the pulsations less marked.

The patient left the hospital on November 2 without any improvement in his general condition, but the pulsating mass continued to decrease in size and finally disappeared altogether. He died about a month later of gradually increasing toxemia and heart failure.

*Comment*—In spite of the one negative blood culture, the diagnosis of subacute infective endocarditis seemed clear in this patient, based on the presence of chills, sweats, the persistence of irregular fever, cardiac enlargement and murmurs, enlargement of the spleen, embolic phenomena in the skin and kidneys and progressiveness of the condition eventuating in death.

The course of events leading up to the formation of the aneurysm was somewhat out of the ordinary. There was no evidence of arterial plugging by an embolus nor disturbance of circulation in the leg. At first the condition was thought to be a femoral phlebitis but later the signs of aneurysm became unmistakable. The most unusual feature was the rapid subsidence and eventual disappearance of clinical evidences of the aneurysm.

The occurrence of the aneurysm during the course of a subacute infective endocarditis, its rapid development and short course are in favor of the nature of the process being mycotic, there is no other reasonable explanation for it. Its situation near the point where the profunda femoris is given off would suggest that an embolus might have been lodged there, but in the absence of definite signs of embolism the question cannot be decided.

*CASE 4—History*—E. R., white, male, aged 18, was admitted to the University Hospital Sept. 10, 1921, complaining of weakness, swelling of the legs and abdomen and palpitation of the heart. At the age of 5, he had a severe attack of acute rheumatic fever that kept him in bed for several months. He was then well until 8, when he had an illness said to be heart trouble with high fever. From this time on, he was never strong and always had palpitation of the heart on exertion. In 1916, he began having attacks of decompensation but recovered fairly well between attacks. The present illness began in April, 1921, and although he has had periods of some improvement, the tendency has been downward. He is very weak and short of breath, his abdomen and legs have become greatly swollen and he suffers from palpitation.

The patient is a Russian Jew and came to this country in 1912. Up to the present attack he had attended school, except during his periods of decompensation.

*Physical Examination*—The boy had a fairly well developed frame but poor musculature. He was distinctly orthopneic. The skin was yellowish and muddy but there was no discoloration of the sclerae. There was generalized edema, involving the legs and flanks particularly. The left arm below the elbow was greatly swollen, owing to thrombosis in the axillary vein. The heart was tremendously enlarged, extending by percussion 6 cm. to the right of the midline, while the apex impulse was felt in the left axilla. The supracardiac dulness was 9 cm. in the first interspace and 11 cm. in the second. In the second left interspace there was an impulse systolic in time. There was a short systolic murmur at the apex and a markedly accentuated pulmonic second sound. The cardiac action was rapid, usually totally irregular, but with



occasional short periods of rapid regular rhythm. There were moist rales at the bases of both lungs, the liver was markedly enlarged and signs of a moderate degree of ascites were present. The blood pressure was 110/75.

Coming from behind the right sternoclavicular joint and extending upward and outward about 3 cm., there was a mass approximately 2 cm. in diameter, apparently just underneath the skin. Over it was seen and felt a violent expansile pulsation, systolic in time. The mass was not tender, the skin was freely movable over it and there was no evidence of inflammation. It could be collapsed by pressure. It divided into two branches, one of which extended outward and the other up into the neck. The pulse in the right brachial and radial arteries was weak but could not be compared with that of the left side on account of the venous thrombosis and great swelling of the left arm.

*Laboratory Examination*—The blood examination showed 5,500,000 erythrocytes, 12,900 leukocytes and 96 per cent hemoglobin. The differential count was normal. The Wassermann reaction was negative. The urine contained a cloud of albumin and many casts, the phenolsulphonephthalein excretion was 25 per cent in two hours and the blood urea nitrogen was 60 mg. per 100 cc. The blood culture remained sterile. Roentgen-ray examination of the chest showed a tremendously enlarged heart but no evidence of aneurysm either of the aorta or the pulmonary artery. Electrocardiograms showed auricular fibrillation with occasional short periods of regular ventricular tachycardia. Pulse tracings made simultaneously over the pulsating mass and the right radial artery showed the upstroke of the pulse wave in the latter approximately 0.25 second later than that obtained over the mass.

*Course*—The patient remained in the hospital ten days. He was given large doses of digitalis with only slight improvement in his condition. At no time was there any elevation of temperature or clinical evidence of active infection. There was no change noted in the mass in his neck. It gave no symptoms and he had not been aware of its presence.

*Diagnosis*—Chronic myocardial disease, probably mitral valvular disease of rheumatic origin, severe cardiac decompensation with passive congestion and edema, auricular fibrillation and paroxysmal ventricular tachycardia, chronic glomerular nephritis, aneurysm of the outer end of the innominate artery.

It was reported to us by the patient's physician, Dr. J. M. Prince, that he died of heart failure ten days after leaving the hospital.

*Comment*—The point of particular interest in connection with the aneurysm observed in this patient is the question of etiology. Aneurysms of any description in patients under 20 are extremely rare. Le Boutillier<sup>25</sup> in 1903, was able to collect only sixty cases. Most aneurysms in the young are either mycotic or due to congenital syphilis. Syphilis did not appear to be a factor in this patient. There were no clinical evidences of the disease and the Wassermann reaction, as stated, was negative. On account of the lack of history of the time of development of the aneurysm, such possibilities as a congenital or traumatic etiology cannot be ruled out altogether. Both, however, are beyond the bounds of probability. On the other hand, the history of severe rheumatism, also an obscure attack of fever with cardiac involvement, the extensive heart disease, the location of the aneurysm at a bifurcation of an artery and the lack of evidence of arterial

disease elsewhere, suggest strongly that the aneurysm owed its origin to an infected embolus from the heart and for this reason is included in the series of cases here reported

#### DISCUSSION

*Incidence and Distribution*—We have collected from the literature all the cases we could find that appear to fall in the group under discussion. Including the four cases reported in this paper, we were able to gather 217 cases. The aneurysms regarded by the older writers as embolic are included, since in most of them, the case reports show clearly that they were really mycotic-embolic. The few cases in which a diagnosis of rheumatic aneurysm of a peripheral artery seem justified are included in spite of the fact that the nature of the rheumatic virus is not established, since their clinical manifestations were similar to those of mycotic embolic aneurysms. The clinical reports of rheumatic aneurysms of the arch of the aorta have been excluded for reasons that will be discussed later.

Arteries in all parts of the body and of various sizes, from the very largest to tiny unnamed vessels (the latter particularly in the brain), may be the seat of mycotic aneurysms. Eppinger has called attention to their multiplicity, stating that it is one of the most constant features of the condition. In this group of 217 cases, more than one aneurysm was found in forty-nine. If complete necropsies had been made in all cases, doubtless many more would have been discovered. The various arteries and their unnamed branches were involved 264 times (Table 1) with a total of 382 plus "numerous aneurysms in three cases." In quite a number of cases, several or many branches of one artery exhibited aneurysms.

The artery most frequently involved is the aorta, sixty-six cases with a total of eighty-eight aneurysms having been found. The favorite site is the root and ascending arch. Next to the aorta, abdominal vessels, namely the superior mesenteric, the hepatic and splenic are attacked, and in these arteries mycotic infection is one of the most important causes of aneurysm. Intracranial aneurysms were found in only thirty-four cases, but the total number of aneurysms was high because of their multiplicity, particularly when small vessels were involved. The middle cerebral and its distribution, particularly the artery of the sylvian fissure was the most frequent situation of the intracranial aneurysms. The arms and legs were almost equally involved, the former in twenty-three and the latter in thirty-one cases. The aneurysms in the extremities were found most often in the large arteries, the femoral and brachial. They are rare in the pulmonary arteries as compared with the systemic, doubtless owing to the compara-

tive infrequency of right sided endocarditis There were only six cases of aneurysm of the pulmonary artery and eight of its branches

*Etiology*—Mycotic aneurysms of intravascular origin always occur in association with some underlying infectious process, usually situated within the cardiovascular apparatus Rarely, they follow blood stream infections from other sources In this series of 217 cases, there was evidence of endocardial disease in 187, the remaining thirty cases occurring in connection with a variety of infections

TABLE 1—DISTRIBUTION OF MYCOTIC ANEURYSMS OF INTRAVASCULAR ORIGIN

Artery	Number of Cases	Total Number of Aneurysms
Aorta	66	88
Innominate	2	2
Vertebral	1	1
Basilar	4	4
Internal carotid	3	3
Anterior cerebral and main branches	3	3
Middle cerebral and main branches	14	23
Posterior cerebral	1	1
Posterior communicating	2	2
Small unspecified intracranial	14	49+ (Numerous in two cases)
Subclavian	1	1
Axillary	3	3
Brachial	10	10
Radial	5	5
Ulnar	5	5
Common iliac	7	7
External iliac	2	2
Internal iliac	1	2
Gluteal	3	3
Femoral	16	17
Profunda femoris	2	2
Popliteal	5	5
Posterior tibial	8	8
Coronary	9	22
Superior mesenteric and branches	24	38
Splenic and branches	15	15
Renal and branches	5	5
Hepatic and branches	19	19
Pulmonary	6	6
Pulmonary branches	8	31+ (Numerous in one case)
Total	264	382+ (Numerous in three cases)

The type of endocarditis usually found is what is commonly called subacute infective or bacterial endocarditis, the endocarditis lenta of Schottmuller, characterized by subacute or subchronic course, luxuriant vegetations on the heart valves, bacteremia and widespread embolism The aneurysms also occur, but less commonly, in other types of endocarditis, varying from highly acute malignant forms of the disease to apparently quiescent lesions The importance of true rheumatic endocarditis, except indirectly as it may offer a favorable site for the development of bacterial endocarditis, is undoubtedly small In cases in which pathologic studies accompany the reports of aneurysms regarded as rheumatic, the findings have resembled more closely those of bacterial than those of rheumatic endocarditis<sup>26</sup> In a few

cases of peripheral aneurysms with embolic phenomena, the course and outcome seemed to justify the diagnosis of rheumatism as opposed to subacute infective endocarditis

In the cases without endocarditis, lung and bone infections have been most often the source of the bacteremia. In ten cases there had been pneumonia, in three, septic lung infection, and in six, osteomyelitis. Other sources of infection were believed to be cystitis, gonorrheal rheumatism, infections of fingers and hands, phlegmonous angina, typhoid fever, influenza and anthrax.

The case for typhoid fever and anthrax is not proven. Four cases of supposed typhoid aneurysms have been reported, two of the aorta, one of the hepatic artery and one of the femoral. In the aortic cases, reported by Gils and Hecker,<sup>27</sup> neither the diagnoses of typhoid fever nor aneurysm could be regarded as substantiated from the evidence presented. In the other two cases reported by Quincke<sup>28</sup> and Cathcart,<sup>29</sup> the diagnosis of typhoid was not established. Oliver's case<sup>30</sup> was the only one believed to be due to anthrax, based on the finding of rods and spores resembling anthrax bacilli in sections of the aneurysm. No cultures were made, nor did the clinical picture and pathologic findings resemble those found in anthrax infections.

Influenzal infections in the form of an influenzal endocarditis may cause aneurysms, cases of this sort having been reported by Weinberger,<sup>31</sup> Horder<sup>16</sup> and Simons.<sup>32</sup> But whether or not the epidemic respiratory infection influenza ever causes aneurysm, is not so clear. Boinet<sup>33</sup> has insisted that it does, but no definite relationship between the infection and aneurysms is evident in the cases cited by him. Johnson<sup>34</sup> recently reported a case of aneurysm of the hepatic artery in a young man in whom symptoms of the aneurysm developed several months after the attack of influenza. This case, by no means conclusive, is the most suggestive thus far reported. It may be noted that the onset of subacute infective endocarditis not rarely suggests influenza and the later development of aneurysm might, therefore, readily be attributed to this infection. There is some evidence that influenza may

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27 Gils. Arch. med. et de pharm. Militaires **22** 102, 1893. Hecker. Deutsch. Mil.-arztl. Ztschr. **22** 1, 1893.

28 Quincke. Berl. klin. Wchnschr. **8** 349, 1871.

29 Cathcart. Southern M. J. **2** 593, 1909.

30 Oliver. Lancet **2** 1033, 1891.

31 Weinberger. Ztschr. f. klin. Med. **62** 456, 1907.

32 Simons. Quart. J. M. **7** 291, 1913.

33 Boinet. Nouveau Traite de Medecine, Maladies des Arteres et de l'Aorte **24** 169, 1913.

34 Johnson. Hospitalstid. **63** 860, 1920.

hasten the development of an aneurysm in an artery previously affected Schelle<sup>35</sup> recorded a case in which rupture of an aneurysm of the descending aorta occurred during an attack of influenza. He believed the aneurysm had been present before the influenza, but that the rupture was due to the settling of the influenzal mycosis in the aneurysm. Huchard<sup>36</sup> observed rapid development of an aneurysm of the aorta in a patient with "gouty aortitis" during the course of an influenzal infection followed by pneumonia.

Malaria was formerly regarded as a cause of aneurysm but this view is no longer held. Possibly, the irregular fever of endocarditis may have occasioned the belief.

*Age and Sex*—The age and sex of patients with mycotic aneurysms is determined by the age and sex incidence of the diseases giving rise to the aneurysms. The age was stated in 174 cases and is summarized by decades in Table 2. The youngest patient was 4 years old and the

TABLE 2—AGE OF PATIENTS ARRANGED BY DECADES

Age	Number of Cases
1-10	14
11-20	50
21-30	57
31-40	32
41-50	14
51-60	5
61-70	1
71-80	1

oldest 78. Most cases occur during the second, third and fourth decades. This is in marked contrast to syphilitic aneurysms which are found most often in the fifth decade. The sex was stated in 178 cases, of which 121 were males and fifty-seven females.

*Bacteriology*—In the cases with endocarditis, there has usually been little difficulty in demonstrating organisms in stained sections of the heart valves, and frequently they have also been found in the aneurysms. But apparently the arterial walls do not furnish so favorable a habitat for them as the heart valves for they tend to disappear from the aneurysms as the latter arrive at more chronic stages. Our Cases 1 and 2 illustrate the fact that organisms may be present in abundance, yet none are to be discovered in the aneurysms themselves.

The organisms most frequently recovered from blood cultures, cultures from the heart valves or from the aneurysms have been streptococci, mostly nonhemolytic types. Staphylococci and pneumococci have also been found a number of times. In at least three cases

35 Schelle. Inaugural-Dissertation Wurzburg, 1893.

36 Huchard. I Pract p 579, 1896.

the influenza bacillus has been cultured and once the gonococcus. Various rod forms have been seen in sections but have not been cultured.

*Pathogenesis*—Mycotic infection of arteries from within, leading to aneurysm formation may occur in the following ways (1) by the lodgment of infected emboli in the lumina of vessels or in the vasa vasorum, (2) by the settling of bacteria on the inner surface of a vessel or in the vasa vasorum, and (3) by continuity or contiguity of infection from the aortic or pulmonic valves.

In the development of mycotic aneurysms beyond the aorta and the pulmonary artery, emboli usually play an important part. The size of the vessel involved depends on the size of the embolus. Rarely, one is large enough to be caught at the bifurcation of the aorta, and in Aitken's case<sup>37</sup> an infected embolus held there was believed to have given rise to an aneurysm. Eppinger has pointed out that mycotic embolic aneurysms are found in situations where emboli are most liable to lodge, namely, the bifurcations of arteries, places where the lumen rapidly narrows or where the vessel makes a sharp turn.

The part usually played by the embolus, so far as aneurysm formation is concerned, is that of bringing infection in contact with the vessel wall. The rôle was well demonstrated in a case reported by Pel<sup>38</sup> in which a soft riding embolus, partly in the femoral and partly in the profunda femoris but not obstructing either vessel, had given rise to beginning aneurysm of the femoral at the point where it lay in apposition to the wall of the artery.

Mechanical injury of vessel walls by emboli is rarely, if ever, more than a minor factor in the production of aneurysms. We have cited above the more recent cases regarded as of purely embolic origin and called attention to the inconclusiveness of the evidence in support of that view.

Aneurysms due to emboli carried through the vasa vasorum are usually found in the ascending arch of the aorta or nearby. Typical cases have been reported by Osler,<sup>2</sup> Eppinger,<sup>3</sup> and J. McCrae,<sup>39</sup> and others. The location of the aneurysms and the close proximity of aortic valve vegetations to the mouths of the coronary arteries in such cases suggests the view that tiny emboli are carried through the coronary arteries to the twigs supplying the region of the ascending arch.

Almost invariably, mycotic embolic aneurysms in the systemic arteries are associated with left sided endocarditis and in the pul-

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37 Aitken Brit M J **1** 1655, 1898

38 Pel Ztschr f klin Med **12** 327, 1887

39 McCrae J Path & Bacteriol **10** 373, 1904-1905

monary arteries with right sided endocarditis Entz,<sup>40</sup> however, reported a case of aneurysm of the pulmonary artery in which there was only mitral endocarditis. An embolus was believed to have been detached from the mitral valve, and to have traveled through a patent ductus botalli to the pulmonary artery. Beatty and Hall<sup>41</sup> observed a case with an obscure septic infection, femoral venous thrombosis, and signs of pulmonary embolism. At the necropsy aneurysms were found in branches of the pulmonary artery and it was suggested that embolism had occurred from the venous thrombosis, although an organized thrombus was found in the right ventricle so that the direct source of the pulmonary embolism remained uncertain.

Direct infection of the inner surfaces of arteries by bacteria circulating in the blood stream is very rare. Uninjured intima is extremely resistant to infection. Clutton and Dudgeon,<sup>42</sup> Edenhuizen<sup>43</sup> and Merke,<sup>44</sup> in their cases of aneurysm, favored the view that infection of the artery had occurred in intimal defects due to preexisting arteriosclerosis. The aneurysms were situated in the midst of patches of arteriosclerosis. Merke found, in addition to aneurysms, verrucose deposits on calcified plaques. Ruge<sup>45</sup> was unable to decide in his case of coronary aneurysm whether infection had begun on the inner surface of the artery or in the vasa vasorum. Moriani<sup>46</sup> found plugs of diplococci within the vasa vasorum, and he believed that infection had arisen by that route in his case. Jordan<sup>47</sup> also believed that the infection, in the aneurysm of the aorta observed by him, had arisen through the vasa vasorum.

Aneurysms due to continuity or contiguity of infection from heart valves occur in the beginning portion of the aorta and the pulmonary artery. In these situations they are found more often than any other type of mycotic aneurysms. It is often impossible to tell which of the two has been responsible for the arterial involvement. Infection by continuity spreads from an aortic or pulmonary valve onto the vessel, producing first an endarteritis, and later, by penetration of infection to deeper layers, an aneurysm. Infection by contiguity is carried directly from the valve to the vessel by the slapping of the infected valve against the artery wall. Trauma may aid in the transfer of

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40 Entz. *Pester med-chir Presse* 47 293, 1911

41 Beatty and Hall. *Proc Roy Soc Med*, London, Path Section, p 147, 1912

42 Clutton and Dudgeon. *Lancet* 1 556, 1908

43 Edenhuizen. *Frankfurter Ztschr f Path* 16 150, 1914

44 Merke. *Schweiz med Wchnschr* 7 122, 1920

45 Ruge. *Deutsch Ztschr f Chir* 80 150, 1905

46 Moriani. Quoted from abstract in *Centralbl f allg Path u path Anat* 21 427, 1910

47 Jordan. *Lancet* 1 515, 1903

infection Libman<sup>48</sup> believes that the impact of a valve containing calcific material against the aorta, even in the absence of infection may cause a small aneurysm

Whether or not aneurysm formation will occur following infection of an artery depends on the extent and degree of destructiveness of the inflammation. If it remains localized to the intima, there may be ulceration but no aneurysm. If it begins in the deeper layers, there may be merely areas of necrosis or abscess formation. Yielding of the vessel is dependent on destruction of the elastic tissue, particularly the internal elastic lamina. If destruction of tissue is very rapid, perforation may occur before the vessel has had time to yield, and there may be free hemorrhage or the formation of a false aneurysm.

Infective lesions may occasionally be indirectly concerned in the formation of aneurysms. In cases reported by Gilewski,<sup>49</sup> and others, aneurysms of the pulmonary artery have followed a high grade mitral stenosis of rheumatic origin. Hart<sup>50</sup> reported an aneurysm of the right sinus of Valsalva with thin translucent walls. He regarded the aneurysm as due to the loss of elasticity in the valve which was the seat of an old inflammation. Kraus<sup>51</sup> also reported an aneurysm in the right sinus of Valsalva, which he ascribed to lack of support from the septum which had been weakened by an old ulcerative lesion just below the valve.

*Pathology*—Mycotic embolic aneurysms are found most often in those cases of infective endocarditis with particularly luxuriant and ragged vegetations on the heart valves. Widespread embolism is usually a feature of these cases, and often other arteries are plugged with emboli beside those in which aneurysms are present. Infarcts in the spleen or kidneys, or both, have also been observed in most cases. Occasionally, at necropsy, emboli can still be found in the aneurysms, and in a few cases it has been possible not only to show their resemblance to vegetations on the heart valves but also to find the places from which they were detached. In most cases, the embolus can no longer be found, probably because of disintegration.

Since most mycotic aneurysms occur before the age of 40 it is usual to find the vascular apparatus in excellent condition, except for the localized mycotic lesions. Many writers have commented on the fact that the arteries in their cases appeared normal until one came on an area of ulceration or an aneurysm with sharply delimited edges

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48 Libman. *Am J M Sc* **144** 313, 1912

49 Gilewski. *Wien med Wchnschr*, p 524, 1868

50 Hart. *Virchows Arch f path Anat* **182** 167, 1905

51 Kraus. *Berl klin Wchnschr* **39** 1161, 1902



This abrupt transition from normal artery to aneurysm is in striking contrast to the condition of the vessels in the neighborhood of syphilitic aneurysms

On account of their widespread incidence throughout the body with different types of tissues surrounding them, and the wide range in the acuteness and destructiveness of the inflammatory processes present, mycotic aneurysms vary greatly in size, appearance and other characteristics. As a rule, they are much smaller than syphilitic aneurysms. It is rare even in the largest vessels to find one bigger than a walnut, except in the case of false aneurysms, which may be much larger. In the small vessels of the brain, they may be the size of a millet seed or a split pea or even smaller. Often they will not be found unless specially looked for on account of their minute size or owing to the fact that their thin walls have become practically disintegrated.

Owing to the destructiveness of the inflammatory processes, mycotic aneurysms are prone to rupture. To this fact, and also the rupture of arteries even before aneurysm formation, is due the large number of false aneurysms found with their sacs consisting of compressed perivascular tissue or sometimes with a layer of adventitia partially surrounding a hematoma communicating with the lumen of a vessel. This type of aneurysm is found most frequently in the peripheral arteries. In such locations as the brain, the abdominal cavity or the arch of the aorta, rupture of an arterial wall is much more liable to be followed by free bleeding, so that the ventricles of the brain, the pericardium, a pleural sac or the peritoneal cavity may be found filled with blood. But even in the mesenteric artery there may be a tiny perforation and the formation of a false aneurysm.

In the aneurysms caused by infection from the heart valves, one is liable to find the same type of inflammatory process in the arterial wall as in the valves. Frequently, vegetations have been observed growing about the edges or in the depths of aneurysms, sometimes they are so luxuriant as actually to fill the sac. As a rule, there is little or no pus formation, but the disintegration of the vessel wall may be fairly rapid, and attempts at repair are pretty much in abeyance. However, in the less active subchronic types of inflammation, reparative processes are more in evidence and the wall of the aneurysm may be definitely thickened as in our Case 1. The aneurysms occurring in bacteremias not associated with endocarditis tend to be more acute and abscesses of the artery wall are more often found. In Vanzetti's<sup>52</sup> case and also in others, the walls of the abscesses that had given rise to the aneurysms

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<sup>52</sup> Vanzetti. Quoted from review by O. Barbacci, *Centralblatt für Pathologie und Anatomie* 19: 984, 1908.

were still present. In these cases the inflammatory process is usually highly destructive and quickly causes disintegration of the arterial wall and perforation.

The intima is usually intact to the edge of the aneurysm and occasionally covers the margin and extends a short distance into the depth of the aneurysmal sac. It is never found intact over the floor of an aneurysm during the active inflammatory stage. Occasionally, when infection begins in the depths of a vessel, there may be rupture of the intima with the formation of a mere slit entirely concealing the aneurysm underneath (Osler,<sup>2</sup> J. McCrae<sup>39</sup>). The combination of endarteritis, ulceration and small aneurysms seem in some cases, particularly in the aorta, may give the vessel a moth eaten appearance (McNeill<sup>53</sup>).

Various stages of the inflammatory process may be found in different parts of the aneurysm, such as healing on one side and recrudescence of infection on the other, leading to enlargement of the sac or to rupture. In cases of multiple aneurysms, destructive processes may predominate in one aneurysm and reparative processes in another. The type of healed mycotic aneurysm described by Eppinger<sup>8</sup> in which the floor of the sac has been covered over by a smooth lining membrane continuous with the intima is apparently very rare, although it had occurred in our Case 2 and to a certain extent in our Case 1. In peripheral arteries, if healing takes place, there is liable to be an obliteration of the aneurysmal sac and the lumen of the artery as well. In Sanne's case calcification of the edges of the aneurysm occurred.

In spite of the tendency of mycotic aneurysms to rupture, arterio-venous aneurysms have been described only by Simmonds,<sup>54</sup> Libman<sup>20</sup> and Floyd.<sup>55</sup> In Simmonds' case there was an aneurysm of the aorta near the bifurcation with a sac that had ulcerated into the right iliac vein. Libman found a communication between the sac of a femoral aneurysm and the femoral vein. In this case the diagnosis of arterio-venous aneurysm was made clinically. Floyd's case was quite similar to Libman's.

Erosion of bone has been reported, so far as we are aware, only once. In this case, described by Libman,<sup>20</sup> an aneurysm of the femoral artery eroded the femur.

*Histology*—The histologic pictures vary as widely as the gross appearances. The most characteristic findings are loss of the intima, destruction of the elastic tissues, particularly the internal elastic lamina,

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53 McNeill Southern M. J. 7 540, 1914

54 Simmonds Munchen med. Wchnschr., p. 627, 1904

55 Floyd Surg., Gynec. & Obst. 33 560, 1921

and acute or subacute periarteritis and mesarteritis. In the more acute cases micro-organisms are often found in enormous masses.

In some cases the transition from uninvolved vessel to the aneurysmal process is abrupt. In others, undermining of the inflammatory process is found out into the vessel wall that grossly appears normal. The intima may be flush with the edge of the aneurysm, destroyed for a distance beyond the dilated area or, on the other hand, may be found extending down a short way into the aneurysm. The elastic tissue is always badly damaged and the internal elastic lamina is destroyed (Fig. 3, Case 2). Apparently, it is weakened by the infection and finally ruptures. The media muscularis may be destroyed either partially or completely, complete destruction occurs more frequently in the smaller arteries. The changes in the adventitia vary from comparatively little damage to complete destruction with the wall of the aneurysm formed by perivascular tissues.

In the more acute aneurysms, there may be marked infiltration with polymorphonuclear leukocytes, microscopic abscesses are not uncommon. In some cases, such as those of Moriam,<sup>46</sup> Klotz<sup>26</sup> and McNeill<sup>53</sup> the inflammatory process seemed to be centered particularly about the vasa vasorum. When the inflammation is less acute, the cellular infiltration may consist of small round and plasma cells which are seen especially in the adventitia and about the vasa vasorum. Often there are many fibroblasts. At a later stage the artery structure is lost and the wall of the aneurysm consists mainly of fibrous tissue. Areas of poorly staining hyaline-like material are found and there may be calcification. The vasa vasorum tend to be thickened and some are entirely obliterated. Fragments of elastic tissue may still be present. Our Case 2 is probably the best instance of repair of a mycotic aneurysm thus far described.

*Clinical Manifestations and Diagnosis*—Usually patients are already under medical observation before the development of mycotic aneurysms, on account of illness, due either to infective endocarditis or some other serious infection. Thus in many cases reported, there has been opportunity to note from the beginning whatever clinical phenomena presented themselves.

In the vessels of the extremities or other superficial arteries where it is possible to study the clinical course of the aneurysms, the most striking feature observed has been their rapid evolution. The onset may occur in a variety of ways. Most frequently the phenomena of embolism are observed first and then in the course of a few days to several weeks aneurysm develops. Embolism, though present, may be overlooked and the condition of the vessel not suspected until a pulsating tumor has manifested itself. Attention is sometimes directed

to a part by pain, on examination there may be only slight swelling or tenderness. Such cases have been mistaken for phlebitis (as in our Case 3), but when tumor and pulsation develop, the error is easily recognized.

Some of the aneurysms rapidly go on to rupture so that the entire course from the beginning of symptoms may last only a week or two, but more often rupture does not occur for several weeks. In peripheral arteries, it may be manifested clinically by rapid enlargement of the tumor which tends to become somewhat boggy and indistinct in outline. Pulsation may still be present. With free rupture, the swelling usually becomes tense and painful. In the cases that do not go on to rupture, the aneurysmal process may become quiescent or apparently healed with a persistence of the tumor and pulsation, as in our Case 4, or as in our Case 3 and Unger's <sup>12</sup> case, the clinical evidences may disappear entirely.

Pain, especially during the period of development of the aneurysm, may be severe, and the part affected may be hot and tender, but these symptoms tend to subside as the process grows older. The tumor in the larger vessels is often stated to be the size of a hen's egg or even larger, but the aneurysms themselves are usually smaller, the mass being made up partly of the surrounding inflamed tissues or sometimes of a hematoma about the aneurysmal sac due to a small rupture. Expansile pulsation is present, often even in false aneurysms. Pulse is usually absent distal to the aneurysm. The circulation in the tissues supplied by the artery affected may be interfered with seriously, but gangrene has been reported in surprisingly few cases.

When superficial arteries are affected, the diagnosis is easy in typical cases. The development of localized tumor and characteristic pulsation along the course of an artery and blockage of blood flow distal to the tumor, occurring in a patient with a septic type of infection, particularly endocarditis, is scarcely to be mistaken for any other condition. It may not be possible to differentiate between true and false aneurysms, but this is of no particular clinical importance. In the early stages, the condition may escape detection or, as stated above, be mistaken for venous thrombosis.

In mycotic aneurysms of the thoracic or abdominal arteries, it is exceptional for signs to develop from which the diagnosis can be made or even suspected. This is to be expected, in view of the small size of most of the aneurysms. The first intimation of the condition may be a sudden fatal hemorrhage and commonly it is, as Jordan found in his case "a post-mortem surprise."

Out of sixty cases in which the root or arch of the aorta has been found at necropsy to be the seat of mycotic aneurysms, our Case 1 is the only one in which a clinical diagnosis was made. The reasons for

this diagnosis have been discussed above. In Sanne's<sup>56</sup> case, a diagnosis of dilatation of the arch was made and in Lauenstein's<sup>57</sup> case, there was believed to be inflammation of the beginning of the aorta but not aneurysm. A clinical diagnosis was made by Baginsky<sup>58</sup> in his case of abdominal aortic aneurysm. The patient developed a pulsating mass in the midabdomen over which a bruit could be heard, previous to which she had shown evidences of septic infection and embolism in the right subclavian artery. In Alexejew's<sup>59</sup> case, there was a palpable pulsation under the umbilicus and the pulse in the left femoral artery was smaller than in the right.

There are to be found in the literature clinical reports of about twenty cases in which the diagnosis was made of aneurysm of the arch of the aorta due to acute rheumatism or chorea. These observations are encountered principally in the French literature, but there are a few from this country and also from Germany. The aneurysms are described as occurring mostly in children or young adults with aortic regurgitation and a history of one or more attacks of rheumatism or chorea. In some of the cases there was thought to be diffuse dilatation of the arch and in others localized ectasis. It is unfortunate that among the patients who died, no necropsies were made. In view of the degree of simple dilatation of the arch that may develop merely as the result of aortic regurgitation, particularly in the young, the diagnosis of aneurysm should be accepted with great caution in such cases, if at all. The most convincing case of the group is the one reported by Bernert<sup>60</sup> in which signs of endocarditis were limited to the mitral valve and the fluoroscope showed spherical dilatation and pulsation of the descending arch.

Aneurysmal dilatation of the pulmonary artery was diagnosed clinically and the diagnosis confirmed at necropsy in cases of mycotic infection of the vessel by Buchwald<sup>61</sup> and Salen<sup>61</sup>. In Salen's case, the roentgen ray showed dilatation of the pulmonary artery, but in Buchwald's case, the diagnosis was made on the clinical findings alone.

Mycotic aneurysm of the mesenteric artery has been diagnosed several times, based on the finding of a pulsating tumor that either could be pushed about the abdomen or might be found first on one side and later on the other, occurring in a patient with infective endocarditis. A bruit over the tumor has also been found of diagnostic value. In one case, masses felt per rectum proved to be mesenteric aneurysms.<sup>20</sup>

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56 Sanne. *Rev. Mens. des mal. de l'enf.* 5: 56, 1887.

57 Lauenstein. *Deutsch. Arch. f. klin. Med.* 17: 242, 1876.

58 Baginsky. *Berl. klin. Wchnschr.* 1: 144, 1908.

59 Alexejew. Quoted from Le Boutilier, *Am. J. M. Sc.* 125: 778, 1903.

60 Bernert. *Ztschr. f. klin. Med.* 69: 121, 1909-1910.

61 Salen. *Acta Med. Scand.* 55: 631, 1921.

One patient was operated on for supposed ruptured gastric ulcer and a bleeding mesenteric aneurysm was found<sup>62</sup> In another case, mesenteric aneurysm was mistaken for abdominal aortic aneurysm

No clinical diagnosis of mycotic aneurysms involving the other abdominal visceral arteries has been reported In hepatic aneurysms the symptoms of pain over the region of the liver, jaundice and bleeding into the gastro-intestinal tract have been observed The occurrence of these symptoms in a patient with a septic infection should strongly suggest the possibility of mycotic aneurysm of branches of the hepatic artery within the liver

Intracranial mycotic aneurysms have not been diagnosed clinically In many cases, no symptoms were discovered that could be related to the aneurysms found at necropsy Clinical signs, when present, have been merely those of embolism, intracranial hemorrhage or both

*Treatment*—Possibility of treatment is limited almost entirely to the aneurysms involving superficial arteries, although in a case reported by Stern,<sup>62</sup> a mycotic mesenteric aneurysm was successfully operated on

The line of treatment to be adopted should be chosen with due regard to the character of the underlying infection When the infection was mild or had already subsided, ligation of the artery affected or extirpation of the aneurysm has been performed several times, apparently with good results, but at least one fatality has been recorded incident to operation in such a case In the cases of typical subacute infective endocarditis with its practically hopeless prognosis, attempts at therapy should be directed mainly toward the comfort of the patient This can often be best secured by avoidance of operative measures Under such a regimen as rest to the part, local applications and sedatives as required to relieve pain, the aneurysms will sometimes retrogress or disappear entirely (as in our Case 3) The old treatment of compression of the artery above the aneurysm has been beneficial in some cases Operation may be necessary for the relief of pain or for rupture of the aneurysm It may also be advisable if the aneurysmal process continues to progress or threatens to rupture For the most part, the results of operation have not been very satisfactory A considerable number of patients have died as a result of the operation or their death has apparently been hastened by it and even those who recovered with a good local result usually died within a short time from their cardiac infection

#### SUMMARY

Three unquestionable cases of mycotic aneurysms of intravascular origin and one in which this diagnosis is probable, are reported The following noteworthy features were exhibited by these cases

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62 Stern Beitr z klin Chir 57 315, 1908

1 Case 1 is the first to be recorded in which a clinical diagnosis of mycotic aneurysm of the arch of the aorta was confirmed at necropsy

2 The aortic aneurysm in Case 2 was healed with replacement of destroyed media and intima by a thin layer of young connective tissue covered over by newly formed endothelium which had grown out from the intima at the edges of the aneurysm

3 In Case 3, all clinical evidences of an unmistakable femoral mycotic aneurysm disappeared

4 In Case 4, there was a violently pulsating but symptomless aneurysm of the innominate artery that appeared to be healed, in a boy, aged 18, without any evidences of syphilis, but with a history of acute rheumatism and an attack of fever with cardiac involvement

The cases of mycotic aneurysm of intravascular origin have been collected from the literature <sup>63</sup> and on the basis of this material and our own, the etiology, pathology and clinical manifestations of the condition are discussed

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63 A complete list of references appears in the reprints

# DISTRIBUTION OF SUGAR IN WHOLE BLOOD, PLASMA AND CORPUSCLES, PERMEABILITY OF RED BLOOD CORPUSCLES FOR SUGAR IN DIABETIC AND NONDIABETIC CASES <sup>†</sup>

HENRY J JOHN, M D

CLEVELAND

A study of the literature pertaining to the distribution of sugar in the blood shows a decided divergence of opinion among different investigators

Tachau <sup>1</sup> found that there was always a higher percentage of sugar in plasma and a smaller percentage of sugar in the corpuscles than in whole blood. In a report of their work on the permeability of the red blood corpuscles to sugar, Gradwohl and Blaivas <sup>2</sup> make the following statement: "When the alimentary hyperglycemia begins and sugar is thrown into the circulation in increased quantity, it is first dissolved in plasma and penetrates the corpuscles secondarily. As the hyperglycemia declines, the sugar content of the plasma goes down and the corpuscles then throw their sugar in excess into the plasma. Tachau attempts to explain by this line of reasoning why it is that in the presence of a declining hyperglycemia of alimentary origin the serum loses its sugar and, strange to say, the corpuscles then hold more sugar than the plasma." The conclusions of Gradwohl and Blaivas were based on twenty-four examinations. They found that the amount of sugar in plasma, in whole blood and in corpuscles was nearly the same. They conclude that their studies, which agree with the work of Tachau, seem to disprove some of the theoretic views of the older physiologists who held that a part of the sugar in the blood was in a state of loose combination with some other substance. This obsolete idea had previously been shattered by the work of Rona and Michaelis, <sup>3</sup> who showed that the blood sugar is in a state of solution and that when diluted blood is shaken with certain colloids, such as ferric chlorid or kaolin, the proteins form a colloidal combination and are absorbed. The proteins can be precipitated quantitatively by the addition of a trace of an electrolyte, but no trace of sugar is removed from the solution by this treatment. If the sugar were united with the proteins it would be carried down with them, and as the reagents used cannot have any

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<sup>†</sup> From the Cleveland Clinic

1 Tachau, H. *Ztschr f klin Med* **79** 421, 1914

2 Gradwohl, R B H, and Blaivas, A J. *J Lab & Clin Med* **2** 416, 1916

3 Rona and Michaelis. *Biochem Ztschr* **16** 489, 1909, **18** 514, 1909



TABLE 1—THE PARTITION OF SUGAR IN THE BLOOD DIABETIC

Plasma Sugar (100%)	Whole Blood Sugar	Per Cent In crease or De- crease	Cor- puscle Sugar	Per Cent In crease or De- crease	Cor- pus- cle Vol- ume	Plasma Sugar (100%)	Whole Blood Sugar	Per Cent In crease or De- crease	Cor- puscle Sugar	Per Cent In crease or De- crease	Cor- pus- cle Vol- ume
114	117	+ 2	117	+ 2		347	321	- 7	300	-13	33
179	183	+ 2	171	- 5	35	279	267	- 4	200	-28	40
400	411	+ 3	352	-12	50	203	210	+ 3	171	-16	40
567	519	- 9	460	-19	55	300	237	-21	242	-20	40
598	578	- 2	464	-22	51	364	354	- 3	272	-25	39
645	598	- 8	500	-22	46	377	420	+11	322	-15	36
579	506	-12	428	-26	52	405	394	- 3	334	-17	41
506	486	- 4	414	-18	52	230	241	+ 5	193	-16	40
424	455	+ 7	364	-14	49	373	335	-10	294	-21	35
98	114	+17			43	437	422	- 3	334	-23	39
124	125	+ 1			45	511	515		400	-21	41
159	136	-15			47	557	530	- 5	444	-20	37
136	131	- 4			46	356	356		300	-16	38
155	172	+11			44	233	229	- 2	179	-23	46
148	159	+ 7			44	323	315	- 3	260	-20	46
286	286		238	-17	54	376	370	- 1	300	-20	46
335	325	- 3				420	384	- 9	310	-26	40
303	363		309	-15	41	265	261	- 1	244	- 8	48
125	394	- 7	375	-12	31	157	175	+12	145	- 8	45
351	381		375	- 2	36	237	214	-10	183	-23	48
309	318	+ 3	263	-15	44	383	360	- 6	250	-34	50
271	262	- 3	230	-15	47	421	401	- 5	374	-11	42
414	394	- 5	353	-15	45	485	485		374	-23	41
391	394		316	-20	44	428	407	- 5	400	- 6	40
425	394	- 8	348	-18	43	273	309	+12	286	+ 4	44
350	350		319	- 9	40	350	350		300	-14	47
302	269	-11	272	-10	42	491	449	- 8	360	-27	44
198	198	- 2	176	-11	45	593	535	-10	444	-25	39
298	254	- 5	250	-16	47	636	610	- 4	526	-17	38
320	307	- 4	261	-18	43	607	596	- 2	512	-15	40
351	351		300	-15	40	530	424	-20	412	-22	47
359	351	- 2	313	-12	41	196	196		178	-11	48
279	263	- 5	230	-17	41	315	285	- 9	219	-30	44
148	204	+38	179	+20	33	356	356		272	-24	44
262	262		224	-15	37	411	411		187	-55	47
285	285		250	-12	35	310	264	-15	214	-31	43
330	319	- 3	300	- 9	37	237	212	-11	176	-26	40
318	302	- 5	272	-14	36	264	268	+ 1	240	- 9	46
260	254	- 2	230	-12	33	460	428	- 7	360	-22	45
129	135	+ 5	122	- 5	43	460	442	- 4	340	-26	43
202	196	- 3	167	-17	43	512	500	- 2	428	-16	42
233	225	- 4			38	428	428		352	-18	42
291	315	+ 8	258	-11	37	342	334	- 2	272	-21	44
308	291	- 5	263	-15	41	250	268	+ 8	200	-20	47
296	312	+ 5	261	-12	42	334	334		294	-12	47
344	328	- 5	256	-25	40	460	408	-11	400	-13	50
449	434	- 3	352	-21	42	214	214		222	+ 3	41
510	506	- 1	384	-23	49	136	145	+ 6	234	+72	
464	506	+12	404	-13	41	230	214	- 7	200	-13	36
210	202	- 4	172	-18	35	250	250		230	- 8	36
262	268	+ 2	230	-12		297	297		206	-30	33
350	350		285	-19	33	155	154		143	- 8	42
379	333	- 7	319	-16	33	286	290	+ 1	219	-24	42
324	315	- 3	256	-21	35	374	334	-10	268	-28	38
115	115		116	+ 1	48	368	366		310	-16	39
145	145		150	+ 3	59	306	250	-18	240	-21	40
209	217	+ 4	196	- 6	43	210	187	-11	176	-16	39
175	170	- 9	180	+ 2	38	192	182	- 5	158	-18	38
86	110	+28	106	-23	43	346	316	- 9	244	-30	40
202	230	+18	224	+11	47	352	334	- 5	294	-16	40
368	312	-15	265	-28	43	280	340	+21	261	- 7	36
324	254	-12	265	-18	44	238	243	+ 2	186	-22	43
355	315	-12	294	-18	43	184	187	+ 2	173	- 6	42

TABLE 2—THE PARTITION OF SUGAR IN THE BLOOD NONDIABETIC

Plasma Sugar (100%)	Whole Blood Sugar	Per Cent In- crease or De- crease	Cor- puscle Sugar	Per Cent In- crease or De- crease	Cor- pus- cle Vol- ume	Plasma Sugar (100%)	Whole Blood Sugar	Per Cent In- crease or De- crease	Cor- puscle Sugar	Per Cent In- crease or De- crease	Cor- pus- cle Vol- ume
89	108	+21	116	+30	38	156	156		105	-33	48
163	182	+11	164	+ 0 5	42	124	125	+ 1	88	-29	42
140	150	+ 7	156	+11	43	124	124		120	- 3	52
128	129	+ 0 5	131	+ 2	45	92	95	+ 3	91	+ 2	41
95	105	+10	134	+41	44	64	84	+31	120	+87	43
98	104	+ 6	104	+ 6	49	98	102	+ 4	104	+ 6	47
94	124	+32	117	+24	38	163	161	- 1	153	- 6	39
155	171	+10	167	+ 8	47	133	132	- 1	120	-10	
188	176	- 6	152	-19	51	131	131		126	- 4	39
168	160	- 5	136	-19	57	53	78	+47	75	+40	36
114	119	+ 5	120	+ 5		72	86	+19	85	+18	39
109	108	- 1	133	+22	48	103	111	+ 8	104	+ 1	35
98	98				48	159			145	- 9	30
146	141	- 3			43	202	209	+ 4	176	-13	34
177	177				39	136	150	+10	127	- 7	35
132	143	+ 8			41	95	95		107	+12	34
75	81	+ 8			45	74	76	+ 3	85	+17	84
98	106	+ 8			41	191	207	+ 8	176	- 8	43
143	137	- 5			43	412	393	- 5	366	-11	42
102	91	-11			41	420	405	- 4	324	-23	44
149	134	-10			45	208	214	+ 5	200	- 2	45
114	123	+ 8			42	80	99	+24	104	+30	41
57	57				45	117	146	+25	101	-11	42
89	100	+12			46	100	110	+10	125	+25	47
101	103	+ 2			37	172	166	- 4	147	-15	37
119	119				39	174	174		162	- 7	32
121	121				44	130	137	+ 5	136	+ 4	37
57	71	+23			30	87	102	+17	107	+23	35
50	63	+26			40	118	119	+ 1	107	-10	37
104	107	+ 2			46	123	143	+16	143	+16	35
164	149	- 3			38	256	210	-18	232	-10	38
121	117	- 3			42	210	384	+82	187	-11	
91	104	+14			40	150	160	+ 7	170	+13	37
50	63	+26			38	63	64	+ 1	113	+80	35
40	51	+28			38	96	109	+14	120	+25	42
111	111				36	128	128		107	-16	39
160	160				36	186	183	- 1	154	-17	47
228	225	- 2			38	204	197	- 4	176	-14	
222	216	- 2			36	205	138	-33	187	- 9	47
69	80	+16			38	125	125		151	+21	50
108	118	+ 9			46	145	112	-23	85	-41	45
131	150	+15			43	125	134	+ 7			51
185	180	- 3			40	183	200	+ 9	187	+ 2	41
106	123	+16			40	172	167	- 3	141	-18	39
79	88	+12			38	162	162		150	- 8	33
67	78	+16			42	107	107		105	- 2	33
126	126					75	88	+18	94	+25	34
148	161	+ 9	128	-14	53	128	120	- 6	124	- 3	42
121	148	+22	128	+ 6	51	207	196	- 5	176	-15	45
116	142	+22	129	+11	50	146	158	+ 8	158	+ 8	35
104	60	-42	104		44	125	133	+ 6	136	+ 9	39
115	79	-31	116	+ 1	51	107	100	- 6	116	+ 8	37
95	102	+ 7	111	+16	35	79	81	+ 2	102	+29	37
167	177	+ 6	150	-10	32	110	111	+ 1	114	+ 3	47
167	177	+ 6			30	150	150		150		47
102	127	+24	146	+44	64	156	143	- 8	141	-10	42
71	79	+11	94	+32	33	136	141	+ 4	206	+50	44
85	116	+37	111	+30	31	106			133	+25	42
94	108	+15	130	+38	42	64	83	+30			35
171	164	- 5	158	- 8	44	125			141	+13	33
175	178	+ 1	172	- 2	47	222	230	+ 3	206	- 7	35
53	53		52	- 2		230	116	-50	236	+ 3	31
78	78				24	155	158	+ 2	200	+29	23
92	109	+18	103	+12	47	104			158	+52	
102	102		94	- 8	52	54	83	+54			38
153	151	- 5	136	-14	52	98	94	- 4	94	- 4	33
104	123	+18	111	+ 7		153	158		156	- 1	38
109	111	+ 1	120	+10	38	121	122	+ 1	122	+ 1	38
65	69	+ 6	100	+54	44	147	136	- 8	129	-12	39
91	104	+14	94	+ 3	55	111	120	+ 8	118	+ 6	35
107	104	- 3	104	- 3	47	82	82		88	+ 7	39

disruptive effect, the proof is complete that it is not possible for the sugar to exist in combination with the proteins

Cammidge <sup>4</sup> states that further evidence of the existence of dextrose in the blood in a free state is furnished by the observation that although charcoal when shaken with a solution containing both sugar and protein absorbs these two substances, it absorbs only the protein when acetone is present. That is, the acetone, being more capable of absorption than the dextrose, prevents the latter from being taken up by the charcoal. Further evidence of this conclusion is also furnished by the results of dialysis experiments

TABLE 3—PERMEABILITY OF RED BLOOD CORPUSCLES TO SUGAR DIABETIC  
Corpuscles Exposed to Action of Glucose 1,000 mg/100 c.c. Made Up in  
Physiologic Solution of Sodium Chlorid

Date	Plasma Sugar	Corpuscle Sugar	2 Hours	Per Cent
April 20	270	202	272	187
		280	544	194
	212	187	576	308
	219	171	526	308
	187	142	600	422
April 20	182	155	544	350
	161		564	350
	280	155	526	339
	204	162	544	336
	187	187	564	302
April 21	171	146	544	373
	129	111	554	499
	236	214	500	234
	330		504	153
	333	316	584	185
April 25	275	333	560	168
	230	316	504	160
	313	248	576	232
	130	124	500	405
	156	150	516	344
	174	145	500	346
	265	230	500	217
	288	252	500	199

Masing has shown by exhaustive experiments that when sugar is added to a quantity of blood in vitro the corpuscles first take up the sugar but later give it up so that most of the sugar is finally found in the plasma. This is a confirmation of the work of Rona <sup>6</sup> and of the earlier work of Masing himself. Masing showed further that the addition of sugar to blood was followed by the slow entrance of sugar into the corpuscles at 0 C. and by a more rapid entrance at 25 C., this entrance being hindered markedly by a high temperature. Masing also showed that treatment of corpuscles with liquor formaldehydi enhanced their permeability for sugar.

<sup>4</sup> Cammidge P. J. Glycosuria and Allied Conditions, Longmans, Greene & Co. 1913 p. 19

<sup>5</sup> Masing E. Arch. f. d. ges. Physiol. **149** 227, 1912

<sup>6</sup> Rona and Doblin. Biochem. Ztschr. **31** 215, 1911

TABLE 4—PERMEABILITY OF RED BLOOD CORPUSCLES TO SUGAR NONDIABETIC  
Corpuscles Exposed to Action of Glucose 1,000 mg/100 cc Made Up in  
Physiologic Solution of Sodium Chlorid

Date	Plasma Sugar	Corpuscle Sugar	1 Hour	Per Cent	2 Hours	Per Cent	3 Hours	Per Cent
April 1	89	92	472	514			500	545
2	97	89	414	466			476	535
7	88	96			544	566		
	152	155			544	353		
	189	162			544	336		
	173	146			460	316		
	83	104			522	502		
	67	75			516	688		
10	125	120			278	232		
	186	170			416	245		
	197	199			464	233		
	124	129			442	343		
11	95	88			428	488		
	183	180			434	333		
	158	186			434	318		
	128	126			424	312		
12	65	72	434	600	444	616	452	630
13	73	73			452	620		
	109	107			454	424		
	105	94			426	453		
	70	78			454	622		

TABLE 5—THE PARTITION OF SUGAR IN THE BLOOD CORPUSCULAR SUGAR

	Number of Cases			
	Increase		Decrease	
	Nondiabetic	Diabetic	Nondiabetic	Diabetic
5 per cent	12	6	10	3
10 per cent	11	1	15	12
15 per cent	6	1	10	23
20 per cent	4	1	5	30
25 per cent	8	1	1	21
30 per cent	5		1	12
35 per cent	1		1	2
40 per cent	2			
45 per cent	2		1	
50 per cent	1			
Above 50 per cent	4			1

TABLE 6—THE PARTITION OF SUGAR IN THE BLOOD WHOLE BLOOD SUGAR

	Number of Cases			
	Increase		Decrease	
	Nondiabetic	Diabetic	Nondiabetic	Diabetic
5 per cent	19	14	15	38
10 per cent	17	4	5	19
15 per cent	5	4		9
20 per cent	6	1	1	2
25 per cent	6	1	1	1
30 per cent		1		
35 per cent	2		2	
40 per cent	1	1		
45 per cent			1	
50 per cent	1		1	
Above 50 per cent	1			

Bailey<sup>7</sup> concludes that blood sugar is divided equally between the plasma and the corpuscles, and that the sugar in the corpuscles bears a direct relation to that in the plasma. Wishart<sup>8</sup> finds that normally the concentration of sugar in the corpuscles is a little below that in the plasma. This discrepancy becomes greater as the amount of blood sugar rises. She did not confirm the statement that in the declining stages of hyperglycemia the corpuscles retain their sugar longer than the plasma, and explains the lower sugar content in the corpuscles on

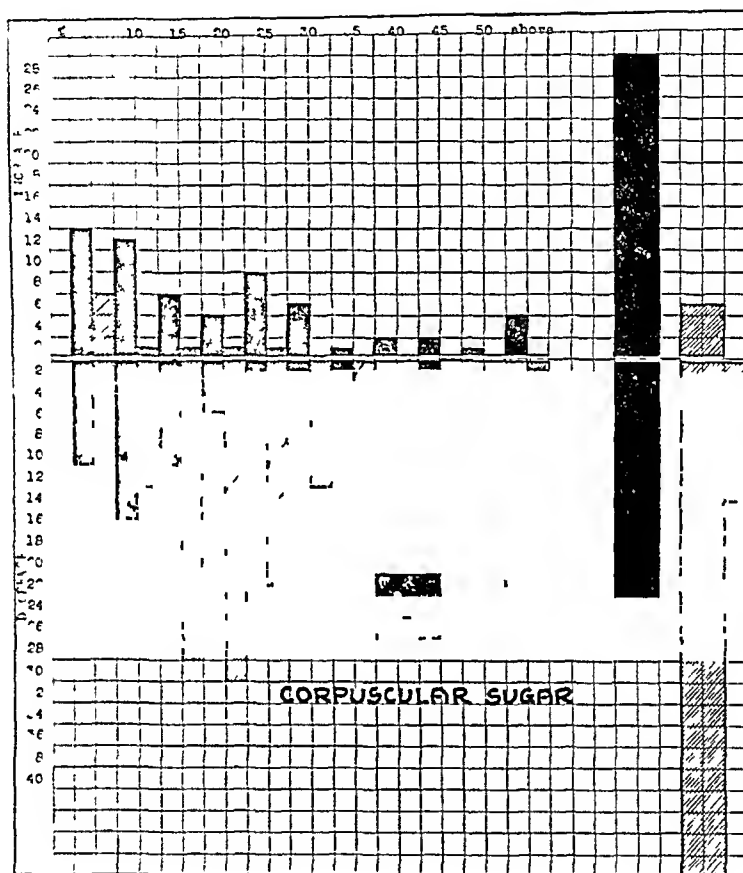


Chart 1—Comparison of the corpuscular sugar in diabetics and in non-diabetics. The solid black and the shaded columns indicate the number of nondiabetic and of diabetic cases, respectively, in which the corpuscular sugar was increased or decreased as compared with the sugar content of the plasma. The cases were grouped according to the percentile increase or decrease as noted at the top of the chart. The sum total of the increases and decreases in each type of case is shown by the black and shaded columns at the right of the chart.

the ground that sugar is more soluble in the plasma than in the corpuscle substance, owing, no doubt, to the lipoidal content of the latter.

7 Bailey, C. V. Arch Int Med 23 455 (April) 1919

8 Wishart, M. B. J Biol Chem 44 563, 1920

The group of cases reported here consists of a series of diabetic and nondiabetic subjects on whom glucose tolerance tests were made. In each case enough blood was taken to allow for estimations of the blood sugar in the plasma and corpuscles as well as in the whole blood. The corpuscles were not washed. The blood was centrifuged at high speed for fifteen minutes after which the plasma was drawn off and 1 c.c. of the corpuscles was taken for sugar estimation. Myers' modification of Benedict's method of blood sugar estimation was used, the readings being made by means of the Kober colorimeter. In all of

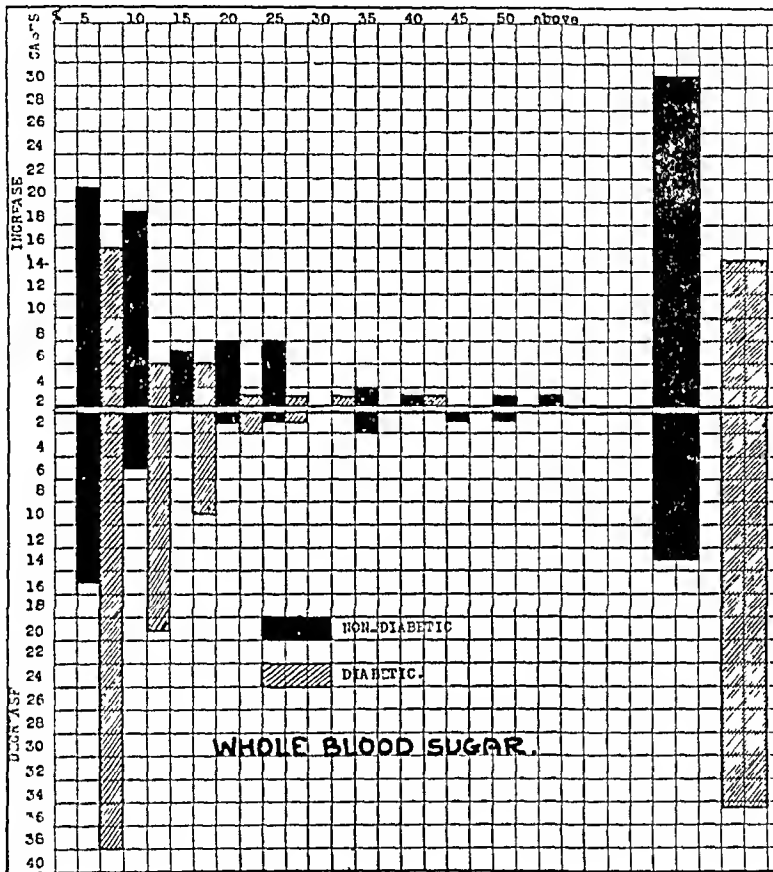


Chart 2—Comparison of the sugar content of whole blood in diabetics and in nondiabetics. The increase or decrease as compared with the sugar content of the plasma is indicated as in Chart 1.

our blood sugar studies the plasma content has been taken as the standard, the estimations of the sugar content of the whole blood and of the corpuscles being compared with this. Thus, any reported increase or decrease in the sugar content of the whole blood or of the corpuscles means an increase or decrease as compared with the plasma sugar.

A comparison of Tables 1 and 2, as illustrated in Chart I, shows that in nondiabetics the average increase in the corpuscular sugar is approximately equal to the average decrease, while in diabetics, in the majority

of cases the corpuscular sugar was decreased. This means that the red blood corpuscles of the nondiabetic may contain either more or less sugar than the plasma while in the diabetic, on the other hand, the corpuscle sugar content is less than the plasma content, higher corpuscle sugar content being exceptional.

The fact that the sugar content of the corpuscles of a nondiabetic is greater than that of the plasma is rather interesting, as in most reports it is stated that the "corpuscular sugar is below that of the

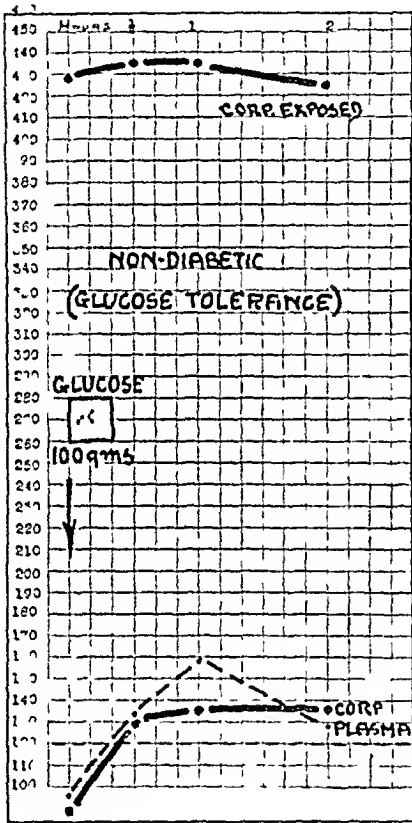


Chart 3

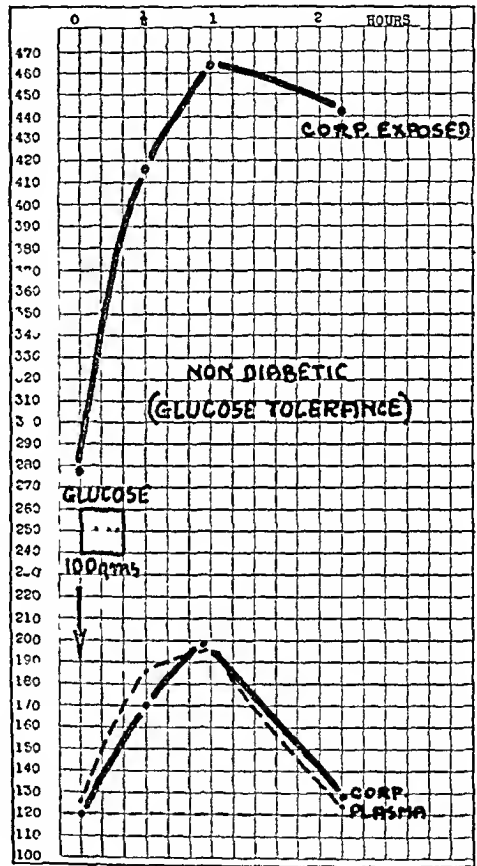


Chart 4

Charts 3 and 4 — Comparison of the glucose tolerance curves of plasma and of corpuscles in nondiabetic cases. The upper curve ("corp exposed") shows the changes in the sugar content of the same corpuscles as those used for the lower curve, after exposure to 1,000 mg per hundred cubic centimeters normal solution for a period of two hours.

plasma," no differentiation having been made between diabetic and nondiabetic patients.

The studies of the sugar content of whole blood (Chart 2) represent the midway stage between the sugar content of the plasma and the corpuscular sugar. This chart and Tables 1 and 2 show that in nondiabetics the average increase in the sugar content of whole blood

is greater than the average decrease, while in diabetics the reverse is true, whole blood sugar content being usually decreased

From these data one would conclude that in the nondiabetic the blood sugar is distributed about equally between the corpuscles and

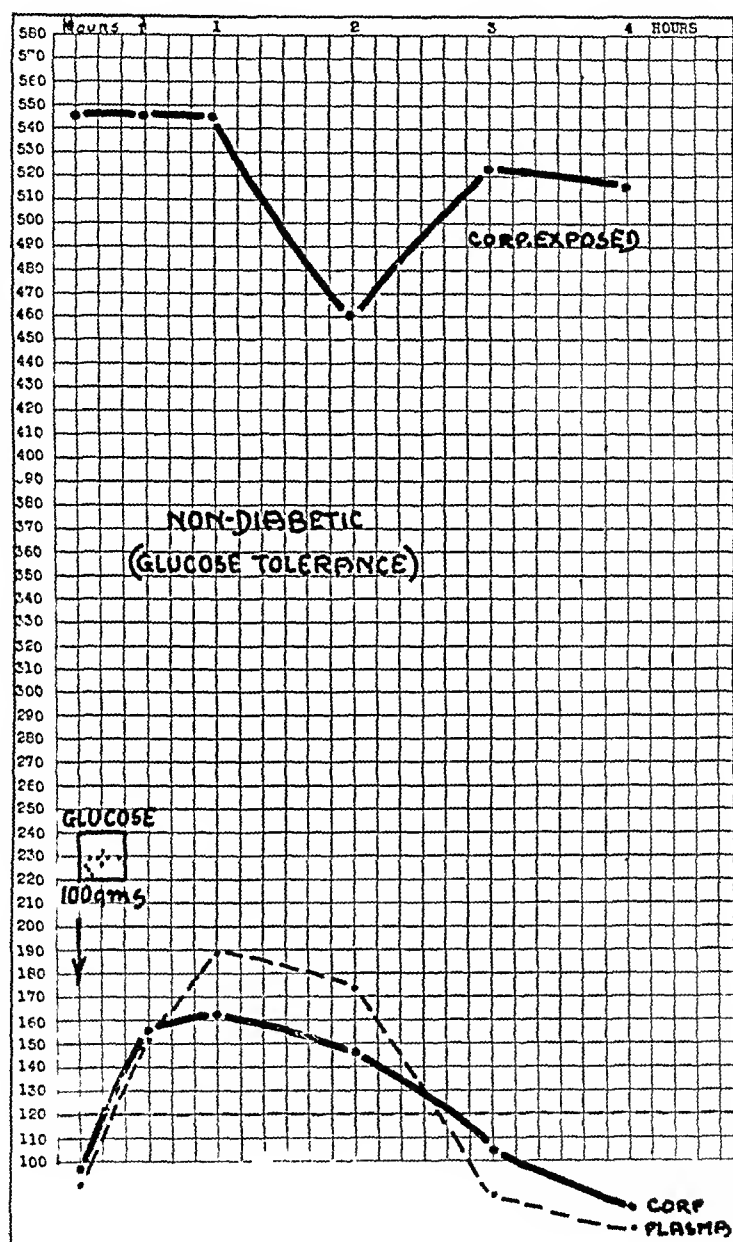


Chart 5—Comparison of the glucose tolerance curves of plasma and of corpuscles in nondiabetic cases. The upper curve ("corp exposed") shows the changes in the sugar content of the same corpuscles as those used for the lower curve, after exposure to 1,000 mg per hundred cubic centimeters normal solution for a period of two hours

the plasma, while in the diabetic, on the contrary, the corpuscles contain less sugar than the plasma which surrounds them. The question which presents itself, therefore, is this: Does this mean that the red blood corpuscles in the diabetic are less permeable to sugar than the



plasma, has the corpuscle membrane been injured in some way so that it is less permeable to sugar just as the renal membrane in untreated cases of diabetes become less permeable to sugar? In attempting to answer this question, my *a priori* reasoning was as follows

If one were to take the red blood corpuscles of a diabetic and those of a nondiabetic, and were to suspend each in a hypertonic solution of

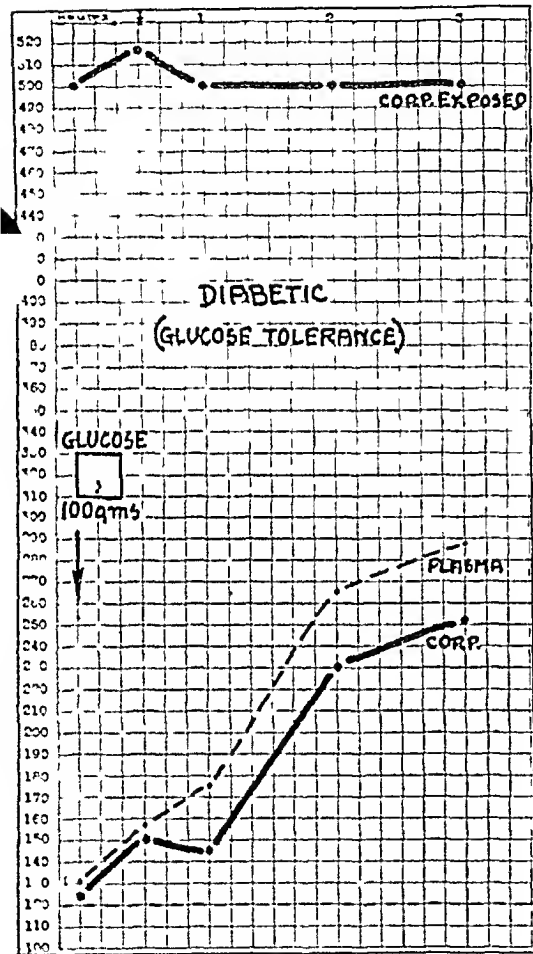


Chart 6

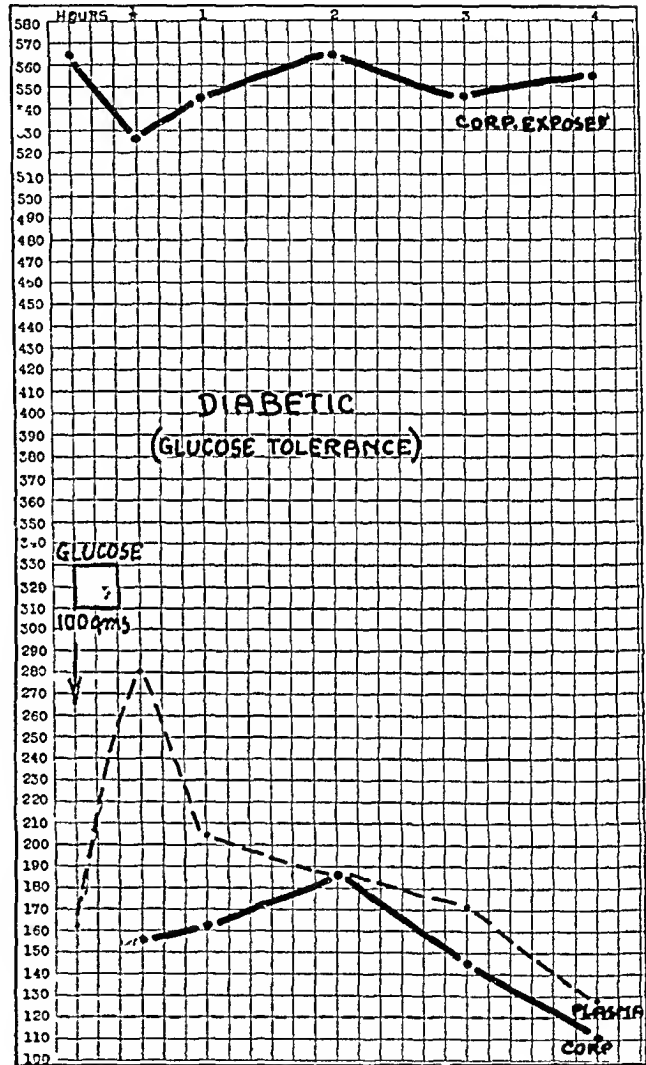


Chart 7

Charts 6 and 7—Comparison of the glucose tolerance curves of plasma and of corpuscles in diabetic cases. The upper curve ("corp exposed") shows the changes in the sugar content of the same corpuscles as those used for the lower curve, after exposure to 1000 mg per hundred cubic centimeters normal solution for a period of two hours

sugar in physiologic solution of sodium chlorid to insure isotonicity, what would happen? If the red blood corpuscles of the diabetic are less permeable to sugar than the plasma, it is logical to suppose that at

the end of a certain period they would contain less sugar than those of the nondiabetic. The following experiment was planned to test the value of this reasoning. Whole blood was centrifuged at a high speed, the sugar content of the plasma and of the corpuscles was determined, the remainder of the red corpuscles were then exposed for a period of

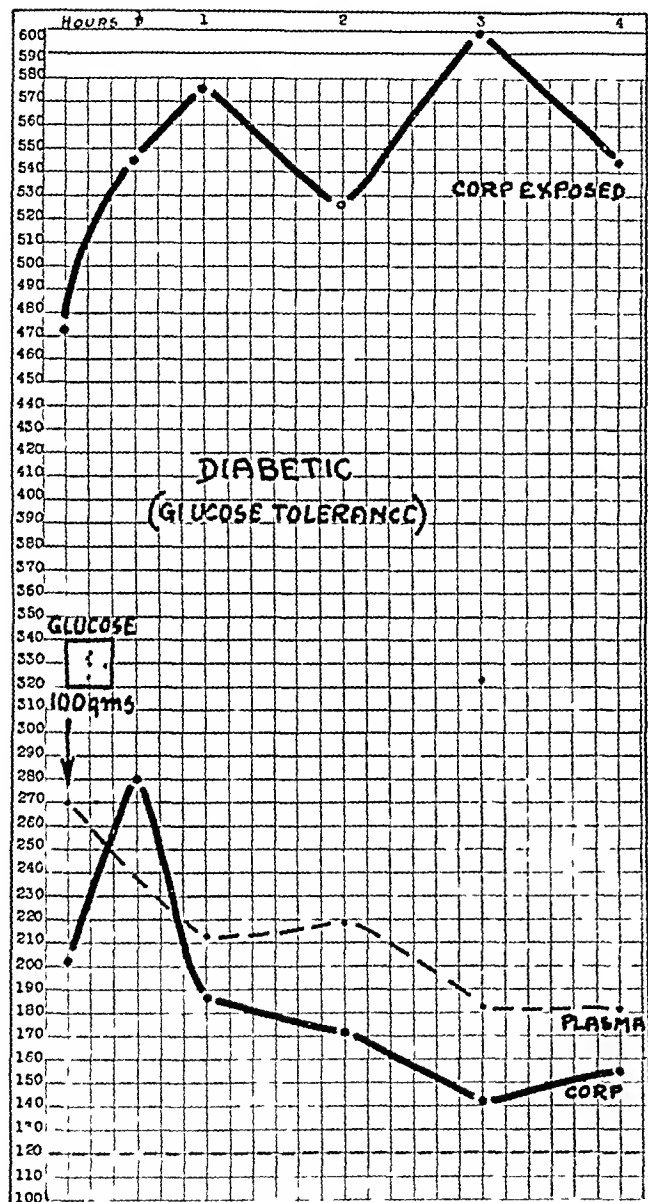


Chart 8

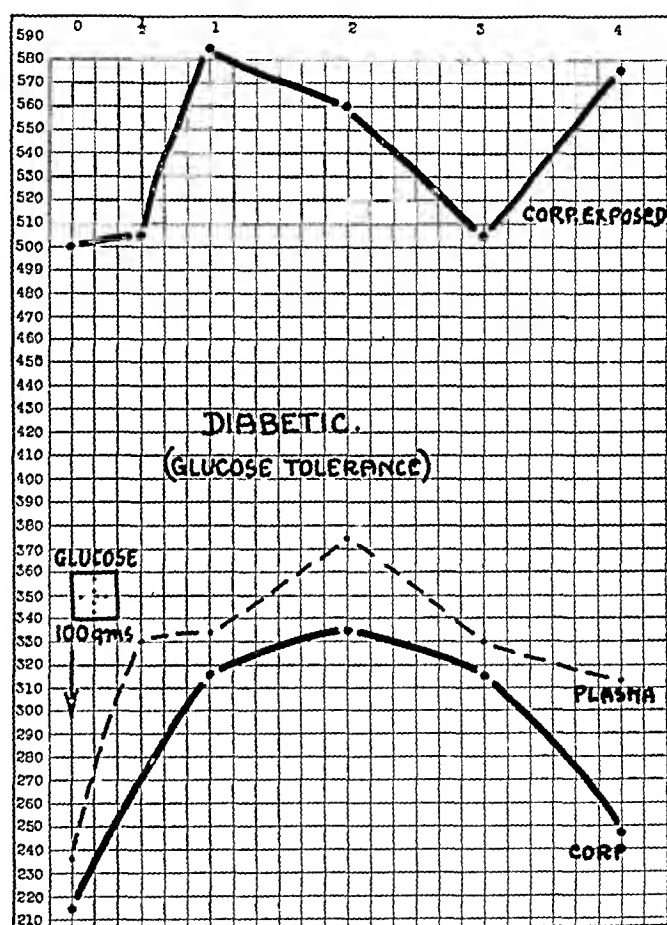


Chart 9

Charts 8 and 9—Comparison of the glucose tolerance curves of plasma and of corpuscles in diabetic cases. The upper curve ("corp exposed") shows the changes in the sugar content of the same corpuscles as those used for the lower curve, after exposure to 1,000 mg per hundred cubic centimeters normal solution for a period of two hours.

two hours to the action of a glucose solution—1 gm to 100 cc of physiologic sodium chlorid solution. At the end of the two hours the corpuscles were centrifuged again at high speed for fifteen minutes and

a sugar estimation was made. The results of the experiment are shown in Charts 3 to 9 and in Tables 3 and 4. As the charts show, with the exception of Case 5, the sugar content of the corpuscles of the diabetics after exposure to glucose solution rose to a much higher level than in the corpuscles of the nondiabetics. An analysis of Case 5 shows that the blood sugar curve (glucose tolerance) returned to the normal level at about the end of the third hour (Chart 5). In this case, therefore, we were dealing with a decreased tolerance, or, in other words, with a prediabetic<sup>9</sup> rather than with a true diabetic.

I am unable to explain this difference between the blood of the diabetic and that of the nondiabetic cases. All I can do is to state the fact that in the blood stream of the diabetic the red corpuscles contain less sugar than the surrounding plasma, and in a strong sugar solution take up more sugar than do the red corpuscles of the nondiabetic. It is my hope that further work may offer an explanation of this phenomenon.

#### CONCLUSIONS

1 In nondiabetics, after the ingestion of glucose, the sugar in the corpuscles may be either increased or decreased as compared with the plasma content, the tendency to an increase slightly predominating.

2 In diabetics the sugar in the corpuscles is practically always decreased below the plasma content.

3 On exposure of the red blood corpuscles of nondiabetics to a concentration of 1 gm of glucose in 100 c c of physiologic sodium chlorid solution for two hours, the corpuscles take up less sugar than the corpuscles of the diabetics which have been treated in a like manner.

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<sup>9</sup> John, H. J. The Prediabetic Stage, *Ohio State M. J.* **17** 826, 1921.

# A STUDY OF BLOOD PRESSURE IN RELATION TO TYPES OF BODILY HABITUS<sup>1</sup>

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Interest in the correspondence of visceral form, position and tonus to bodily habitus as observed in gastro-intestinal roentgen-ray studies suggested the analysis of some available data as to the relation of blood pressure to bodily habitus

The conceptions of bodily habitus as followed in this analysis are those formulated by Mills,<sup>1</sup> and they are used in the classification of the subjects of this study The sthenic type (Fig 1) is of strong skeletal build, short and deep thorax, relatively broad shoulders, a costal angle of 90 degrees or more, and has a narrow pelvis as between the anterior superior spines of the ilia The hypersthenic type (Fig 2) is an accentuation of all the sthenic characteristics, giving a massive build, with short, deep and broad thorax, an obtuse costal angle and narrow pelvis The torso is massive above The asthenic type (Fig 3) is of delicate skeletal build, with long and narrow thorax, very acute costal angle and wide flare of pelvis The torso is large below The hyposthenic type (Fig 4) follows closely the sthenic characteristics, but these are not so definite and the general build is less rugged

Classification is made difficult by transitional types All subjects are not pure sthenics or asthenics, and classification by the external topographic criteria only assumes that topography and tonicity are inseparable in their hereditary transmission

Stillé cites the movable tenth rib as a positive stigma of the asthenic constitution However, Kastner,<sup>2</sup> in a small group of cases selected by this sign, found no constant agreement between it and the asthenic form and position of the stomach It is conceivable that heredity can endow a person with topographic characteristics tending toward the sthenic type, but hold a dominant asthenic characteristic of tonicity

The subjects for this study were unselected applicants for factory work, and their previous occupation is unknown Classification of each subject was made prior to taking his or her blood pressure The blood pressure readings were all made under uniform conditions, at the same time of day, with the same mercury column instrument, the subject in the sitting posture, using the right arm, and by the auscultatory method

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\* Read before the Washington University Medical Society, May 8, 1922

1 Mills, R W The Relation of Bodily Habitus to Visceral Form, Position, Tonus and Motility, *Am J Roentgenol* 4 155 (April) 1917

2 Kastner Movable Tenth Rib as an Enteroptotic Stigma, *Arch f klin Chir* 117 737, 1921



Figure 1



Figure 2

Fig 1—The Sthenic Habitus (From Mills, courtesy of Am J Roentgenol)

Fig 2—The Hypersthenic Habitus (From Mills, courtesy of Am J Roentgenol)



Figure 3

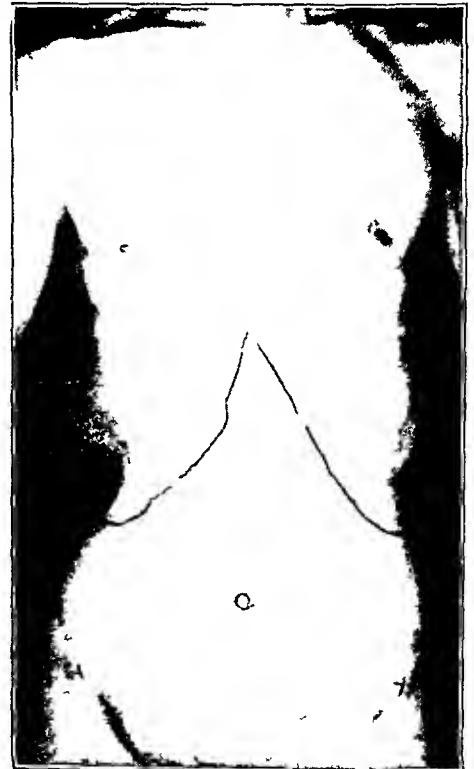


Figure 4

Fig 3—The Asthenic Habitus (From Mills, courtesy of Am J Roentgenol)

Fig 4—The Hyposthenic Habitus (From Mills, courtesy of Am J Roentgenol)

TABLE 1—MALES BLOOD PRESSURE VARIATIONS OF DIFFERENT TYPES

Blood Pressure Mm Hg	Hyper- sthenies 2, Num ber	Sthenies, 82		Hyposthenies, 76		Asthenies, 19		Total, 179	
		Num ber	Per Cent	Num ber	Per Cent	Num ber	Per Cent	Num ber	Per Cent
Systole									
151-160		3	3.6					3	1.6
141-150		5	6.1	1	1.3			6	3.3
131-140	2	18	21.9*	5	6.5			25	13.9
121-130		31	37.8	16	21.1	2	10.5	49	27.4
111-120		17	20.7	36	47.3	2	10.5	55	30.7
101-110		8	9.7	14	18.8	13	68.3	35	19.5
91-100				4	5.2	1	5.2	5	2.8
81-90						1	5.2	1	0.5
Diastole									
91-100	1	3	3.6					4	2.2
81-90		23	28.0	4	5.2			27	15.0
71-80	1	38	46.3	27	35.5	1	5.2	67	37.4
61-70		12	14.6	36	47.3	11	57.8	59	32.9
51-60		5	6.1	9	11.8	7	36.8	21	11.7
41-50		1	1.2					1	0.5

\* Bracketed percentages indicate the groups selected for analysis in Table 3

TABLE 2—FEMALES BLOOD PRESSURE VARIATIONS OF DIFFERENT TYPES

Blood Pressure Mm Hg	Hyper- sthenies, 1, Num ber	Sthenies, 106		Hyposthenies, 69		Asthenies, 62		Total, 238	
		Num ber	Per Cent	Num ber	Per Cent	Num ber	Per Cent	Num ber	Per Cent
Systole									
151-160		1	0.9					1	0.4
141-150	1	2	1.8	1	1.4			3	1.2
131-140		12	11.3	8	11.6	2	3.2	22	9.2
121-130		45	42.4*	11	15.9	4	6.4	60	25.2
111-120		27	25.4	34	49.2	16	25.8	77	32.4
101-110		14	13.2	13	18.8	28	45.2	55	23.1
91-100		6	5.6	2	2.9	11	17.7	19	8.0
81-90						1	1.6	1	0.4
Diastole									
91-100		3	2.8					3	1.2
81-90		14	13.2	8	11.6	1	1.6	23	9.6
71-80	1	51	48.1	29	42.0	16	25.8	97	40.8
61-70		32	30.2	25	36.2	36	58.0	93	39.1
51-60		5	5.6	7	10.1	8	12.9	21	8.8
41-50						1	1.6	1	1.2

\* Bracketed percentages indicate the groups selected for analysis in Table 4

TABLE 3—MALES ARITHMETICAL AVERAGES OF CENTRAL GROUPS

Group Total (Selected According to Blood Pressure)	Total	Average Age	Blood Pressure			Body Surface, Sq M
			Systole	Diastole	Pulse	
Sthenies	82		111-140	61-90		
	100%		80.4%	88.9%		
Hyposthenies	76		101-130	61-80		
	100%		87.2%	82.8%		
Asthenies	19		101-110	51-70		
	100%		68.3%	94.6%		
Total Selected						
Sthenies	65		126.3	78.8	47.5	1.81
Hyposthenies	67		116.3	71.7	44.6	1.67
Asthenies	15		106.8	63.3	43.5	1.663
17-20 Years						
Sthenies	7	18	123.1	76.6	46.5	1.703
Hyposthenies	15	18	116.3	68.7	47.6	1.65
Asthenies	7	17.7	104.6	61.7	42.9	1.61
21-30 Years						
Sthenies	23	25.6	125.6	76.2	49.4	1.83
Hyposthenies	28	25.3	117.0	71.7	45.3	1.658
Asthenies	4	24.2	106.5	65.5	41.0	1.72
31-40 Years						
Sthenies	23	36.6	126.4	81.2	45.2	1.834
Hyposthenies	15	34	115.0	72.9	42.1	1.746
41-50 Years						
Sthenies	11	45	129.2	77.3	51.9	1.772

Tables 1 and 2 are numerical tabulations of the charts and show in comparative percentages the downward blood pressure variation of the different types from sthenic to asthenic

The bracketed percentages indicate the groups selected for analysis (Tables 3 and 4) and represent the central portions of the incidence curves, the extremes of the incidence in the high and low pressures being discarded

TABLE 4—FEMALES ARITHMETICAL AVERAGS OF CENTRAL GROUPS

Group Total (Selected According to Blood Pressure)	Total	Average Age	Blood Pressure			Body Surface Sq M
			Systolic	Diastolic	Pulse	
Sthenics	106		101-130	61-80		
	100%		81.0%	78.3%		
Hyposthenics	69		101-130	61-80		
	100%		83.9%	78.2%		
Asthenics	62		91-120	61-80		
	100%		88.7%	83.8%		
Total Selected						
Sthenics	68		118.4	73.4	45.0	1.61
Hyposthenics	55		115.6	72.3	43.3	1.589
Asthenics	51		105.7	68.2	37.5	1.506
17-20 Years						
Sthenics	43	17.7	118.5	71.9	46.6	1.58
Hyposthenics	38	17.8	114.0	70.3	44.7	1.53
Asthenics	30	17.9	103.5	66.9	36.6	1.499
21-30 Years						
Sthenics	23	24.5	118.0	75.6	42.4	1.66
Hyposthenics	14	22.8	119.7	77.3	42.4	1.56
Asthenics	18	23.1	109.0	69.6	39.4	1.51
31-40 Years						
Sthenics	2	33	120.0	80.0	40.0	1.64
Hyposthenics	3	34.8	117.3	73.3	44.0	1.56
Asthenics	3	34.6	108.0	73.3	34.7	1.56

TABLE 5—HABITUS CLASSIFICATION

	Females		Males		Total		Mills' Percentage of 1,000 Cases Males and Females
	Number	Per Cent	Number	Per Cent	Number	Per Cent	
Hypersthenic	1	0.4	2	1.1	3	0.8	4.7
Sthenic	106	44.5	82	45.8	188	45.1	48.1
Hyposthenic	60	29.0	76	42.4	136	34.6	35.4
Asthenic	62	26.1	19	10.6	81	19.4	11.8
	238		179		417		

Tables 3 and 4 show arithmetical averages for the large central portions of the blood pressure incidence of the different types, and a further separation into groups for age

There is no significant blood pressure variation between the types associated with then age variation

There is a definite, though very small, direct correspondence in body surface variation and the decreasing pressure between the types

Table 5 compares the type percentages in my group to the percentages of a group of 1,000 gastro-intestinal cases, as given by Mills

3 Mills R W Two Tables Pertaining to the Incidence of Bodily Habitus and the Time of Complete Gastric Motility in Different Types of Habitus Am J Roentgenol 9 731 (Nov ) 1922

The variation in the type percentages between the male and the female groups suggests that the commonly accepted difference in the male and female blood pressure is due to the predominance of the asthenic type among females, which increases the incidence of lower pressures and hence lowers the averages

Tables 6 and 7 show in comparative percentages the incidence of subjects in each type according to differences of 0.1 square meter of

TABLE 6—INCIDENCE OF MALES IN EACH TYPE

Body Surface, Sq M	Hypersthenic, Number	Sthenic		Hyposthenic		Asthenic		Total	
		Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
2.31-2.40	2							2	1.1
2.21-2.30									
2.11-2.20									
2.01-2.10		3	3.6					3	1.6
1.91-2.00		3	3.6					3	1.6
1.81-1.90		12	14.6	1	1.3	1	5.2	14	7.8
1.71-1.80		18	21.9	18	23.6	3	15.8	39	21.8
1.61-1.70		28	34.1	19	25.0	3	15.8	50	27.9
1.51-1.60		13	15.8	20	26.3	8	42.1	41	22.8
1.41-1.50		5	6.1	14	18.4	2	10.5	21	11.7
1.31-1.40				4	5.2			4	2.1
						2	10.5	2	1.1
	2	82		76		19		179	

TABLE 7—INCIDENCE OF FEMALES IN EACH TYPE

Body Surface, Sq M	Hypersthenic, Number	Sthenic		Hyposthenic		Asthenic		Total	
		Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
2.31-2.40									
2.21-2.30		1	0.9					1	0.4
2.11-2.20		0						0	
2.01-2.10		2	1.8					2	0.8
1.91-2.00		3	2.8					3	1.2
1.81-1.90		10	9.4					10	4.2
1.71-1.80	1	12	11.3	1	1.4	3	4.7	17	7.1
1.61-1.70		26	15.1	15	21.7	10	16.1	51	21.4
1.51-1.60		20	28.3	32	46.3	19	30.6	81	31.0
1.41-1.50		19	17.9	20	29.0	21	33.8	60	25.2
1.31-1.40		3	2.8	1	1.4	9	14.5	13	5.4
	1	106		69		62		238	

body surface. Body surface was determined by the nomographic chart of Boothby and Sandiford<sup>4</sup>. There is a slight decrease in the body surface from the sthenics to the asthenics of this group.

#### SUMMARY

In a group of 417 factory workers the blood pressure is analyzed for its relation to bodily habitus. In this group the sthenic habitus is accompanied by a higher blood pressure than is the asthenic habitus. The pressure accompanying the hyposthenic habitus is intermediate.

<sup>4</sup> Boothby, W. M., and Sandiford, R. B. Nomographic Charts for the Calculation of the Metabolic Rate by the Gasometer Method, Boston M. & S. J. 185:337 (Sept. 22) 1921.



The average blood pressures are approximately the same for the male and female asthenics, being 106.8 mm systolic and 63.3 mm diastolic for the males and 105.7 mm systolic and 68.2 mm diastolic for the females.

The pressures for the hyposthenic groups are also approximately the same, 116.3 mm systolic and 71.7 mm diastolic for the males and 115.6 mm systolic and 72.3 mm diastolic for the females. The sthenic group shows a higher pressure for the males, 126.3 mm systolic and 78.7 mm diastolic, compared to that of the females 118.4 mm systolic and 73.4 mm diastolic.

These relations do not change when the types are separated into groups for age decades.

There is a very small direct correspondence between the types for body surface and the decreasing blood pressure.

# HEMOGLOBINURIA IN HEMOLYTIC JAUNDICE \*

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My purpose in presenting this paper is to supplement the evidence in favor of the occasional occurrence of spontaneous hemoglobinuria in hemolytic jaundice. Three cases of this type in which the diagnosis of hemolytic jaundice is well established and an occasional case of questionable diagnosis have been reported in German and French. However, I have been unable to find a case reported in the English literature. In view of the rarity of the condition and the interesting phenomena which are associated with the mechanism of hemolysis, the case which I shall report is of more than ordinary interest.

## REPORT OF CASE

*History*—Mrs A F (Case A 354493), an extremely pale, somewhat jaundiced, short, stout woman, aged 32 years, presented herself for examination in April, 1921. She had enjoyed unusually good health until she had suffered a moderately severe attack of influenza three and one-half years before. Convalescence had been protracted but seemed to be complete, with the exception of pallor and probably slight icterus. Nine months before, she had become definitely weaker and more anemic and dyspneic on exertion. Six months before, she had had an attack of diarrhea and vomiting. In one week she developed marked jaundice and began to pass highly colored urine. The stools were said to have been of normal color. She improved somewhat on medical treatment at her home but for the last few weeks she had been more anemic and more jaundiced. Her appetite had remained good, in fact her weight had gradually increased. On two or three occasions, without apparent cause, following a day or two of weakness, depression, headache and increasing jaundice, the urine had become dark for a day or two.

*Examination*—The patient was obese, weighing 186 pounds, and very anemic, her skin had a lemon yellow hue. The liver and spleen did not seem to be enlarged, examination was difficult, however, because of the patient's obesity. Examination of the eyegrounds showed somewhat dilated and tortuous veins, and one or two rather large irregular hemorrhages in the periphery, not however, the type of hemorrhage usually seen in pernicious anemia. The hemoglobin was 25 per cent, the erythrocytes were 1,060,000, giving a color index of 1.1, the leukocytes were 3,800. A relative lymphocytosis was present, and an occasional normoblast. There were slight anisocytosis and poikilocytosis. The blood picture was suggestive of pernicious anemia. However there was no glossitis. Two test meals showed slight hyperacidity and the neurologic examination was entirely negative.

In the absence of characteristics of pernicious anemia the existence of hemolytic jaundice was immediately suspected, in spite of the fact that marked splenic enlargement was not present. It is to be noted also that the color index very rarely exceeded 1, subsequent counts gave the color index varying from 0.6 to 0.9.

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\* From the Section on Medicine, Mayo Clinic

\* Presented before the Association of American Physicians, Washington, D C, May 4, 1922

Examination of the duodenal contents was attempted but was unsuccessful because of lack of cooperation. The calcium time and prothrombin time were prolonged, but otherwise the various coagulation tests and the bleeding time were normal. The platelet count was 92,000. Purpura was not present. Two tests showed an increased fragility of the erythrocytes. The reading each time was 0.5 for initial hemolysis and 0.38 for complete hemolysis with control at 0.42 for initial and 0.34 for complete. The first specimen of urine examined did not show albumin or casts. Later a small amount of albumin was often present and occasionally a large amount. Casts were not found. The blood sugar was 0.12 mg for each 100 cc. Examinations of the stools were negative for parasites and ova. There was no indication of loss of blood.

Evidence could not be obtained that members of the family had had jaundice, splenomegaly, or diseases of the blood.

While the patient was under observation, one month after admission, a severe crisis with hemoglobinuria occurred without apparent cause. An immediate examination of the blood serum showed hemoglobinemia. A cystoscopic examination made at this time revealed bilateral hemoglobinuria with very dark chocolate-colored urine coming from both ureters. Specimens of urine from the ureters did not contain erythrocytes. Horse serum (12 cc serum, 6,000 units of antitoxin) seemed to check this attack of hemoglobinuria within three days.

*Course*—During April, May and June, three transfusions were given. In June the patient's erythrocytes were 2,260,000, and hemoglobin was 45 per cent, the highest in the course of our observation. She maintained a fairly good condition during the summer. In August, 1921, the erythrocytes again dropped to 1,580,000 without the occurrence, however, of hemoglobinuria. The patient was very weak but had a ravenous appetite.

A thorough investigation for syphilis was made at this time with negative results. An examination of the cerebrospinal fluid was negative. A therapeutic test of five doses of neo-arsphenamin was given without apparent improvement; one of the treatments was followed by a reaction consisting of cardiac pain, dizziness, fever and syncope, which may have been partly due to the concomitant onset of hemoglobinuria. It was learned afterward that the jaundice had begun to deepen before the neo-arsphenamin was given.

The patient had four protracted attacks of hemoglobinuria while under our observation and her condition became very low with each. The onset of the attacks was with malaise, weakness, mental depression, headache and slight fever. Within a day or two the jaundice deepened and within three or four days the hemoglobinuria appeared. Although the patient had nausea and abdominal distress, she had never had an attack of gallbladder colic. During attacks she felt very ill largely because of general prostration and headache, although she did not seem to be in serious condition. Besides these severe crises she often complained of milder attacks of nausea, weakness, headache, and a deepening jaundice without hemoglobinuria. In other words, her attacks of hemoglobinuria seemed to be superimposed on the crises of hemolytic icterus.

*Treatment*—At various times, coagulen (Ciba), horse serum, ox serum, calcium by mouth, and transfusions were given in attempts to check the hemoglobinuria. In general, these agents seemed to fail in this effect, although it is possible that horse serum and ox serum may have been of some value.

During one of the patient's remissions she was given a cool bath without the development of hemoglobinuria. At one time, ice bags were placed over the loins with no deleterious effect. The patient said that she had often taken cool baths and that being chilled from exposure had no effect in causing an attack. She did not believe that exposure or exertion in any way played a part in initiating attacks. In fact hemoglobinuria occurred while she was at absolute rest and carefully guarded from exposure in the hospital, it seemed most likely to occur after satisfactory improvement in the blood. Whenever the erythrocytes rose approximately to 2,000,000, an attack was likely to occur.

This was repeated so often that eventually the patient dreaded improvement as much as she dreaded the prostration of severe anemia for fear of another crisis with hemoglobinuria

*Resumé*—The important features of this case were (1) slight jaundice and anemia which had probably existed for three years, (2) marked jaundice and anemia of six months' duration, (3) crises similar to those of hemolytic jaundice without, however, gallbladder colic, (4) a blood picture which at times approached that of pernicious anemia, (5) the presence of bile in the stool and its absence from the urine save in crises, (6) a markedly increased fragility of the erythrocytes on two examinations, (7) an increased reticulated cell count, (8) seven severe crises which were associated with hemoglobinuria, in one of which hemoglobinemia and bilateral hemoglobinuria were demonstrated, (9) the absence of any effect of cold or exposure on the occurrence of the hemoglobinuria, (10) the absence of hemoglobinuria after transfusion, and (11) the recurrence of the hemoglobinuria when the erythrocytes reached approximately 2,000,000

In 1900, Bettman<sup>1</sup> gave an excellent description of a case of hemolytic jaundice with hemoglobinuria. The attacks of hemoglobinuria occurred with some of the acholuric crises. Bettman's patient, a man, aged 29 years, first seen April 3, 1899, had been jaundiced since childhood and had had "nose bleed" occasionally for many years. There was no evidence of syphilis. The spleen was considerably enlarged, there was a definite history of crisis associated with very dark urine. Blood pigment and a few erythrocytes in the urine had been reported one year previously. Jaundice was brought on by overeating and overdrinking, by physical exertion, by emotional excitement, and especially by cool weather. Hemoglobinuria was not produced by placing the hands in ice water, although the urine contained a few erythrocytes and hemoglobinemia was demonstrated. Splenectomy was not performed and necropsy is not reported.

In 1908, Chauffard and Troisier<sup>2</sup> described a case of hemolytic icterus which was accompanied by attacks of hemoglobinuria. This might be regarded as a transition case between acquired hemolytic jaundice and jaundice of congenital origin, for the patient had always been pale, but had developed jaundice late in life. There was no family history of jaundice. In 1901, there had been slight jaundice, in 1902, after a fit of anger, jaundice had been marked and after that constant. In 1906, the patient had been operated on by Koch and the liver found to be normal, while the gallbladder contained thickened bile with bile sand, but no calculi. Six months later, the biliary fistula closed but jaundice persisted. Three times without chilling, and with increased jaundice, there had been an attack of fever and the urine became "malaga colored." Spectroscopic examination revealed the presence of

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1 Bettman. Ueber eine besondere Form des chronischen Ikterus, *Munchen med Wchnschr* **47** 791, 1900

2 Chauffard, A. and Troisier, J. Deux cas d'ictère hemolytique, *Bull et mem Soc med d hop de Par* **2** 411, 1908

hemoglobin in the urine, urobilin was abundant. Examination of the stool revealed an excess of stercobilin. The fragility of the erythrocytes was increased from 0.50 to 0.46. The reticulated cell count was increased to 12 and 14 per cent. The erythrocytes fell to 1,000,000. The spleen had been found to be slightly enlarged, the liver was not palpable.

Hijmans van den Bergh,<sup>3</sup> in 1911, reported a similar case, that of a man, aged 47 years. The family history was negative. The jaundice had been present for twelve years. Attacks of hemoglobinuria had occurred for six years. During the attacks the patient became very ill and anemic but had maintained a fairly satisfactory condition between times. This patient eventually developed severe anemia with high color index. The erythrocytes became reduced to 1,156,000. The stools were normal in color and there was no bile in the urine. Increased fragility of the erythrocytes was demonstrated and the reticulated cell count was high, 18 per cent. A diagnosis of hemolytic jaundice seems to be well established in spite of the fact that the spleen was not demonstrably enlarged. The patient was not followed to operation and the article contains no report of the subsequent course of the case.

Donath and Landsteiner,<sup>4</sup> Hoover and Stone,<sup>5</sup> and others have demonstrated that the hemolysis in paroxysmal hemoglobinuria is due to an autohemolysin which combines with the erythrocytes after a mixture of the patient's serum and his own or another's erythrocytes is cooled, when the mixture is warmed to body temperature, hemolysis occurs. The red corpuscles themselves are not altered (Hoover and Stone). Complement is necessary in the cooling mixture. Zinsser<sup>6</sup> concludes that there is considerable variation in the mechanism even in paroxysmal hemoglobinuria due to chilling.

The mechanism of hemolysis in the hemoglobinuria of hemolytic jaundice is probably quite different from that of paroxysmal hemoglobinuria due to chilling. Widal has called attention to the fact that experimental hemolysis caused by chemical poisons results in icterus if the dose is small, and in hemoglobinuria if the dose is large. It is likely that in hemolytic jaundice there is a constant destruction of

3 Hijmans van den Bergh, A. A. Ictere hemolytique avec crises hemogloburiques, fragilite globulaire, *Rev de med* **31** 63, 1911.

4 Donath, J., and Landsteiner, K. Weitere Beobachtungen uber paroxysmale Hamoglobinurie. *Centralbl f Bakteriologie, Parasitologie u Infekt* **45** 204, 1908.

5 Hoover, C. F., and Stone, C. W. Paroxysmal Hemoglobinuria, *Arch Int Med* **2** 392 (Sept.) 1908.

6 Zinsser, H. Infection and Resistance, an Exposition of the Biological Phenomena Underlying the Occurrence of Infection and the Recovery of the Animal Body from Infectious Disease. New York, Macmillan Co. 1914.

erythrocytes continuing over a period of years. This slight destruction permits the change from hemoglobin to bilirubin in a normal manner, the presence of icterus doubtless means an increase of destruction which can be partially cared for possibly by the endothelial system, but which cannot be properly eliminated by the liver, the presence of hemoglobinuria means a still greater and probably very sudden increase in hemolysis.

Pearce<sup>7</sup> has placed the limit of hemoglobin which may be free in the blood of the dog before hemoglobinuria occurs as 0.06 gm for each kilogram of body weight. Sellards and Minot,<sup>8</sup> in 1916, in a very important piece of experimental work estimated the tolerance to the intravenous injection of hemoglobin of normal persons and of persons with the various types of anemia. Very much less hemoglobin was required to produce hemoglobinuria in hemolytic jaundice than in the anemias secondary to hemorrhage.

It may be that a renal factor is also present. Gilbert and Lereboullet,<sup>9</sup> in 1900, discussed the possible occurrence of a "renal form of simple acholuric icterus." Silvestri,<sup>10</sup> in 1921, concluded that the kidney may secrete substances which have a destructive action on erythrocytes within its vessels. An excellent summary of this viewpoint has been published by Cumston.<sup>11</sup> There may be, therefore, in hemolytic jaundice with hemoglobinuria a renal factor, besides sudden, severe hemolysis, which consists of either a reduction of the renal threshold or an actual hemolytic process in the kidney itself.<sup>12</sup>

Ashby<sup>13</sup> has made immunologic studies in a case of hemolytic jaundice (Case A387430) now under my observation, which in its clinical aspects is almost identical with the one herewith reported, save that hemoglobinuria has occurred only after each transfusion and not spontaneously. The patient's blood was in Group II. Ashby tested the patient's serum against his own corpuscles and against Group II corpuscles from a normal person, with and without icebox incubation.

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7 Pearce. Hemoglobinuria, Monographic Med, New York, D Appleton and Company 1 573, 1916

8 Sellards, A. W., and Minot, G. R. Injection of Hemoglobin in Man and Its Relation to Blood Destruction, with Especial Reference to the Anemias, J. M. Research 34 469, 1916

9 Gilbert, A., and Lereboullet, P. La forme rénale de l'ictère acholurique simple (albuminurie intermittente, albuminurie continue, hemoglobinurie paroxystique), Bull et mem Soc med d hôp de Par 9 662, 1901

10 Silvestri, T. Del fattore renale in certi casi di emoglobinuria parossistica Policlinico 28 1203, 1921, abstr J. A. M. A 77 1291 (Oct 15) 1921

11 Cumston, C. G. Clinical Notes from France. The Splenorenal Theory of Paroxysmal Hemoglobinuria, New York M. J. 110 812, 1919

12 Widal, M. Discussion, Bull et mem Soc med d hôp de Par 2 418, 1908

13 Ashby, W. P. Personal communication

Tubes were incubated in the icebox for one hour, and at 37.5 C for one and one-half hours with negative results. The dilution of serum to corpuscles was 20 to 1. The action of the serum was therefore strikingly different from that which has been reported in connection with paroxysmal hemoglobinuria.

From a study of both the clinical and the immunologic data the conclusion seems justifiable that the hemoglobinuria of hemolytic jaundice is not due to syphilis, that it is not brought on by exposure to cold, and that the mechanism of hemolysis is not analogous to that in paroxysmal hemoglobinuria due to chilling.

# THE RELATION OF AGE AND OBESITY TO VITAL CAPACITY \*

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In view of the frequent association of dyspnea with obesity on the one hand, and the close relationship of dyspnea with vital capacity on the other hand, it seemed of interest to learn the values of the vital capacity in obese individuals. However, with the exception of a casual mention by Myers<sup>1</sup> of the relation of age and obesity to the vital capacity of the lungs nothing was found in available literature.

Hutchinson,<sup>2</sup> in 1846, first studied the vital capacity of normal persons using the spirometer of which he was the inventor. He found that the vital capacity varied more closely with the height than any other body measurements. Until recent years the procedure has not been extensively applied to clinical medicine, but now, because of amplification and refinement of the original work of Hutchinson, it is conceded to be of some importance in diseases affecting the chest organs. Peabody and Wentworth<sup>3</sup> applied the test to cardiac patients and found that such patients regularly showed a decreased vital capacity when dyspneic, ranging in amount from 40 per cent in the badly decompensated cases to nearly normal in compensated lesions.

Dreyer<sup>4</sup> considers vital capacity to be of great value in the assessment of physical fitness, his work has been done largely in the English Army, and the standards used by him have been mostly based on the height of the trunk taken in the sitting posture. Lundsgaard and Van Slyke,<sup>5</sup> and also Myers and Dreyer<sup>6</sup> have shown that there is a slight decrease in vital capacity in pulmonary tuberculosis, which tends to improve after treatment. It has also been determined by a number of investigators that the vital capacity is reduced in emphysema, asthma, bronchiectasis, hydrothorax and pneumonia. In cases of great physical weakness, but without diseases of either heart or lungs Peabody and

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\* From the Department of Laboratories and the Medical Clinic of the Buffalo General Hospital.

1 Myers, J. A. The Value of Vital Capacity Readings in Clinical Medicine, *Minnesota Med* **4** 635 (Nov) 1921.

2 Hutchinson J. *Med Chir Tr* London **29** 137 1846.

3 Peabody, F. W., and Wentworth, J. A. Clinical Studies of the Respiration. IV The Vital Capacity of the Lungs and Its Relation to Dyspnea, *Arch Int Med* **20** 443 (Oct) 1917.

4 Dreyer, G. The Assessment of Physical Fitness, New York, Paul B Hoeber.

5 Lundsgaard, C., and Van Slyke, D. R. *J Exper M* **27** 65, 1918.

6 Dreyer, G. and Burrell, L. S. T. *Lancet* **1** 1212 (June 5) 1920.



Sturgis<sup>7</sup> have found readings of only 26 per cent below the normal. These observers also state that fatigue of the muscles of respiration produced no reduction in vital capacity in cases of heart disease.

It is clear that for a study of the vital capacity in obesity, a normal standard would be required for comparison. The normal standard in common use, however, is based on the vital capacity of persons mostly between the ages of 20 and 30 years. Obviously, the age of a maximum fitness cannot be applied as a standard for all ages. It was, therefore, decided to test the vital capacity of a series of normal persons in order to determine the required normal standard.

#### METHODS AND STANDARDS

The vital capacity spirometer designed by Peabody and manufactured by Sanborn and Company was used in making all of the tests. The highest of three readings were taken as the vital capacity and more than one observation was made whenever it was thought necessary.

The standards used have been those suggested by West,<sup>8</sup> being based both on height and surface area, the latter being estimated from the height and weight using the formula of DuBois and DuBois.<sup>9</sup> The vital capacity of normal persons is expressed in percentage based on surface area in Chart 1, and by both height and surface area in the tables, and the others both on surface area and height. For height, the normal standard is determined by multiplying the height in centimeters by 25 c c for men and 20 c c for women. For surface area, the standard is the product of multiplying the surface area in square meters by 2.5 liters for men and 2.0 liters for women.

#### DISCUSSION OF NORMALS

This group contains 184 persons varying in age from 15 to 85 years. They consist of average normal persons, who are largely of sedentary occupations, including students, physicians, nurses, hospital employees, convalescent surgical patients, and medical patients without disease of the heart or lungs and without physical weakness. The senile group was mostly obtained in homes for the aged. They were able to walk about and had only such disease as is incident with their age, e. g., arteriosclerosis, emphysema, and possibly calcification of the

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7 Peabody, F. W. and Sturgis, C. C. Clinical Studies of the Respiration. VII. The Effect of General Weakness and Fatigue on the Vital Capacity of the Lungs. *Arch. Int. Med.* 28: 501 (Nov.) 1921.

8 West, H. F. Clinical Studies on the Respiration. VI. A Comparison of Various Standards for the Normal Vital Capacity of the Lungs. *Arch. Int. Med.* 25: 306 (March) 1920.

9 DuBois, D. and DuBois, E. F. Clinical Calorimetry. Fifth Paper. The Measurement of the Surface Area of Man. *Arch. Int. Med.* 15: 868 (May) 1915.

costal cartilages Of the 184 persons studied, 120 fell between the ages of 15 and 50 Of these, 67.5 per cent were between 90 and 110 per cent, 25.8 per cent were below 90, and 6.6 per cent were above 110 per cent with the surface area standard Up to the age of 50 years, the average vital capacity was 95.8 per cent, then it gradually reached 50 per cent at the age of 85 years, the greatest fall in any decade being between the ages of 50 and 60 years Chart 1 serves to show this curve of vital capacity percentage with relation to age and may be of value in estimating the normal vital capacity, especially beyond the age of 50 years It would seem that the standards used by West were entirely satisfactory for practical purposes up to the age of 50 The average vital capacity of this group was about 4 per cent lower than the normal series studied by West, which may be accounted for by the

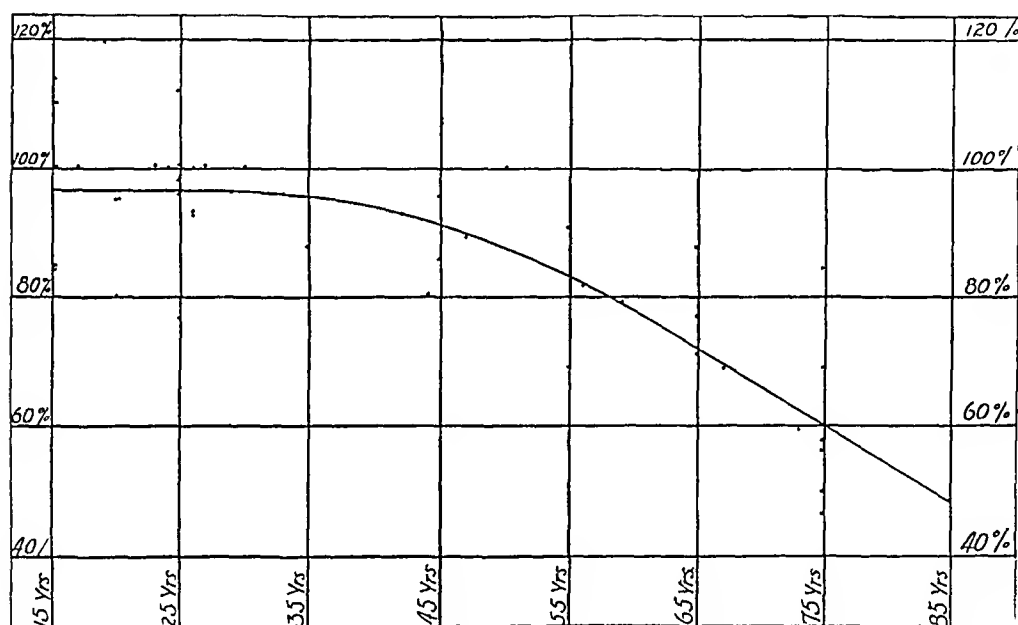


Chart 1—Vital capacity of 184 normal patients according to age, using surface area standard

fact that his subjects were mostly well developed men and women between the ages of 20 and 30

There are doubtless many factors producing a reduction in vital capacity after the age of 50, but in the absence of definite disease all must be considered as manifestations of a normal aging process They possibly constitute such conditions as loss of elasticity of the alveoli, immobility of the thorax, weakened general musculature and myocardium, and lack of exercise

#### DISCUSSION OF OBES E SUBJECTS

This group comprises 32 persons who were definitely obese, twenty-seven were women and five were men Another smaller group made

up of twenty-four people, twenty of who were women and four men, who were not definitely obese but who were distinctly "overweight," is also presented This grouping was rather arbitrary and was based on an impression gained on physical examination In the obese group most of the persons weighed over 80 kg and in the "overweight" group under that figure with lower limit represented by a person who weighed 64 kg and whose height was 152 cm As far as could be determined, none of these people had disease of the heart or lungs, although the majority complained of some degree of dyspnea It is interesting in this connection to note that the most pronounced case, a woman aged 33 years, weighing 198.2 kg, did not have dyspnea, and had a vital capacity by height of 87.7 per cent and by surface area of 53 per cent Her activities were necessarily slow and restricted, which might have been a factor

The dyspnea that occurs in cases of obesity may be due to several factors The frequent association of obesity with coronary sclerosis

TABLE 1—OBESSE CASES IN DECADES

	Ages	Average Vital Capacity to Height Standard, per Cent	Average Vital Capacity to Surface Area Standard, per Cent	Number of Cases
	20-30	96.5	82.1	6
	30-40	90.5	71.9	8
	40-50	84.6	71.6	9
	50-60	72.0	62.0	6
	60-70	68.5	53.2	2

and myocarditic changes is well known Yet, the excessive accumulation of fat in the pericardium may in itself lead to atrophic changes in the heart muscle and, consequently, to insufficiency of the latter However, in young and especially muscular persons, it may require a long time for such secondary changes to be brought about, during which time the obese subject may enjoy good health as far as his cardio-respiratory apparatus is concerned

Between the ages of 20 and 30, only six obese persons were studied Of these, four were under 100 per cent by the height standard and all by the surface area standard In this group (Table 1), the vital capacity was essentially normal by the height standard between the ages of 20 and 30, dropping slowly to the age of 50, where there was a rather sudden reduction of 12 per cent, behaving about as normal persons do Only two subjects had a vital capacity above 100 per cent by the height standard The vital capacity according to surface area was considerably reduced, as would be expected, there being an average difference from the height standard of 14.3 per cent Although the curve of reduction according to age follows much the same course as

in the case of normal people, there was a tendency for the vital capacity of obese individuals to be reduced even by the height standard. However, between the ages of 15 and 50 the average vital capacity in the normal group was 95.8 per cent, and in the combined obese and "overweight" groups, 75.8 per cent by the surface area standard and 88.8 per cent by the height standard. In estimating the vital capacity of obese and "overweight" people it is probably better to use the height standard or make a correction by adding 20 per cent to the surface area standard, this being the difference between the normal vital capacity and that of the obese and "overweight" groups.

Chart 2 represents the vital capacities of the obese and "overweight" groups for all ages, in order of weight, beginning with the heaviest. The ( ) indicates the percentage according to height and the (x) according to surface area.

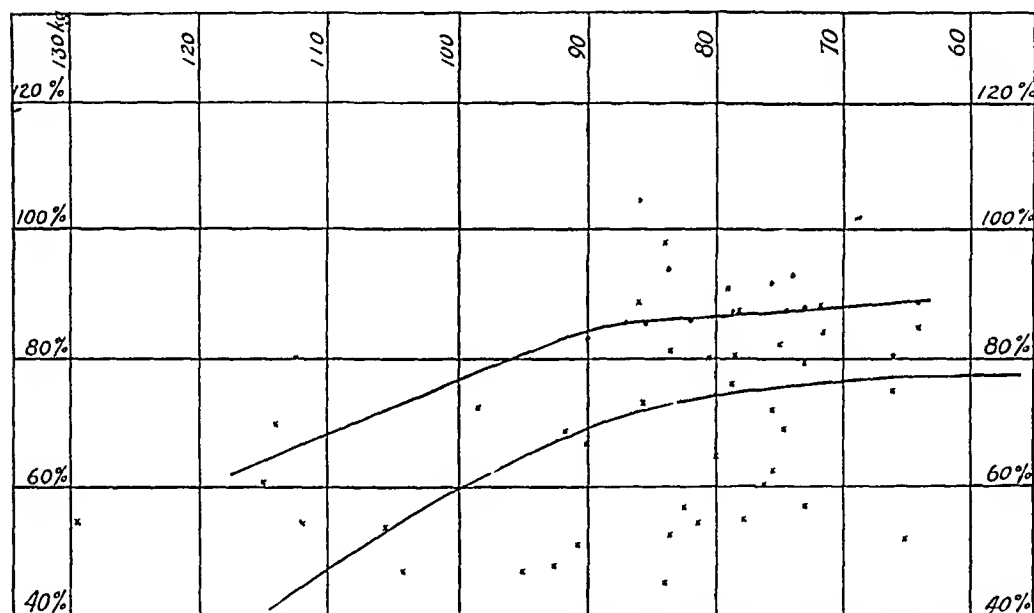


Chart 2—Vital capacity of obese class beginning with heaviest • = per cent height, x = per cent surface area

according to surface area. It will be seen that there is a slight tendency for the vital capacity to increase as the weight decreases.

In Table 2, six obese cases are grouped separately from the normal obese group, because of the diagnosis of "chronic myocarditis." All had symptoms of a cardiac nature of from 3 to 15 years' duration—dyspnea, palpitation and easy fatigue—and all had a slight vascular hypertension. None of this group was decompensated and but one had slight edema. The vital capacities of all were between 50 and 60 per cent by the height standard and 40 and 50 per cent by that based on surface area. A corresponding group of cardiac patients would not, judging from the work of Peabody, have shown this degree of reduction. However, if the correction of 20 per cent be added to the surface

area percentage the result would be about what one would expect in such cases

One patient, a girl, aged 18, who had acromegaly, and who weighed 90 kg, most of the increase having taken place in the past two years, had a vital capacity of 130.5 per cent by height and 109.4 per cent by surface area. This case was not included in the obese group as she was considered as being distinctly pathologic. This, by the way,

TABLE 2—OBESE CARDIAC CASES

Age	Sex	Weight, kg	Height, cm	Surface Area Square Meters	Vital Capacity C c	Vital Capacity to Height Standard, per Cent	Vital Capacity to Surface Area Standard, per Cent
51	F	97.0	157.0	1.96	1,700	54	43
45	F	94.9	156.5	1.94	1,850	59	47
45	F	77.8	154.5	1.77	1,820	59	52
45	F	85.0	164.0	1.92	1,700	52	44
43	F	92.1	153.0	1.69	1,800	57	48
42	F	113.3	164.5	2.21	1,850	56	42

TABLE 3—OVERWEIGHT CASES IN DECADES

Age	Average Vital Capacity to Height Standard, per Cent	Average Vital Capacity to Surface Area Standard, per Cent	Number of Cases
20-30	84.5	77.0	6
30-40	83.8	76.9	4
40-50	88.6	75.5	7
50-60	76.2	68.3	7

TABLE 4—EFFECT OF WEIGHT REDUCTION ON VITAL CAPACITY

Case	Date	Weight kg	Age	Vital Capacity in C c	Per centage Height Standard	Percentage Surface Area Standard	Remarks
F F	12/21/21	84.7	31	3,730	115.1	98.0	No dyspnea
	4/20/22	74.5		3,800	117.2	106.1	General improvement
R C	6/ 8/21	78.5	29	3,000	91.0	80.0	Dyspnea +
	4/22/22	67.2		3,000	91.0	87.8	Dyspnea absent
C S	9/23/21	114.9	20	2,700	82.2	61.9	Dyspnea +
	4/21/22	100.1		3,600	109.7	87.3	Dyspnea absent, general improvement
M K	2/20/22	73.6	50	2,300	75.6	67.2	Diabetes, dyspnea +
	4/19/22	62.5		2,600	85.5	81.7	Dyspnea not noticeable, general improvement

may, perhaps, be accounted for by the actual increase in the bony framework of the thorax, as such cases sometimes show

Table 3 shows twenty-four cases arranged in decades, the subjects were not considered obese but were "overweight." Like the other groups of normal and obese subjects, the vital capacity makes a rather precipitant drop after the age of 50 years, averaging 12 per cent. The average vital capacity is similar to the obese group, being reduced by the surface area standard and only slightly so by the height standard.

Table 4 shows a study of four patients, two obese and two "overweight." Their weights were reduced by dietary measures for the

TABLE 5—NORMALS

Age	Sex	Weight, Kg	Height, Cm	Surface Area Square Meters	Vital Capacity C c	Vital Capacity Percentage Height	Vital Capacity Percentage Surface Area
15	+O+						

TABLE 5—NORMALS—(Continued)

Age	Sex	Weight, Kg	Height, Cm	Surface Area Square Meters	Vital Capacity Cc	Vital Capacity Percentage Height	Vital Capacity Percentage Surface Area
28		76.7	176.0	1.56	2,900	92.9	92.9
29		49.5	164.5	1.52	2,950	89.6	97.0
29		69.0	164.5	1.75	3,400	103.0	97.1
29		71.0	172.0	1.84	4,500	104.6	97.8
29		41.5	171.5	1.31	2,050	67.6	78.2
29		71.5	180.0	1.95	4,000	88.8	81.9
29		67.5	148.0	1.61	3,200	108.0	99.3
30		41.9	161.0	1.40	2,800	86.9	100.0
30		60.7	173.0	1.73	3,400	79.0	79.0
31		33.6	165.1	1.57	3,200	96.9	101.5
31		66.5	166.0	1.74	3,200	96.3	91.9
31		72.0	179.5	1.91	4,650	108.8	97.4
32		71.2	168.5	1.81	4,900	116.3	108.4
32		40.6	160.5	1.38	3,200	80.0	93.0
32		66.6	167.0	1.75	3,450	103.2	90.8
32		42.1	161.5	1.40	3,250	100.0	116.0
33		62.0	157.5	1.63	3,650	92.6	89.6
33		66.5	181.0	1.85	4,000	88.5	86.5
33		56.3	164.3	1.61	3,100	94.2	96.2
34		44.2	153.0	1.50	2,700	88.2	90.0
35		73.5	160.5	1.83	2,700	84.0	88.0
35		42.7	153.0	1.36	3,000	98.0	110.2
36		47.5	139.0	1.46	3,100	97.4	106.1
36		76.4	157.5	1.87	3,000	95.2	95.5
37		69.8	173.0	1.83	4,100	94.9	89.7
37		74.2	173.5	1.88	4,200	96.7	89.3
38		45.9	171.5	1.39	2,200	72.6	74.0
38		51.4	154.5	1.47	2,000	93.8	88.6
38		67.9	186.5	1.91	4,500	96.5	94.3
40		58.1	184.0	1.77	4,300	94.0	97.0
40		74.2	167.5	1.83	3,200	95.5	87.5
40		62.7	172.0	1.74	3,600	104.6	103.4
41		51.8	159.5	1.51	2,300	72.0	76.0
41		45.2	157.5	1.42	2,700	85.7	95.0
42		64.2	154.5	1.63	3,050	98.7	98.5
42		66.1	158.5	1.67	2,900	91.0	86.0
42		75.2	165.5	1.82	3,100	93.6	85.1
43		47.0	165.5	1.74	4,500	108.6	103.4
44		48.9	151.5	1.43	2,800	92.4	98.1
44		70.0	171.0	1.82	3,800	91.3	80.3
45		49.3	159.0	1.48	2,550	80.1	86.9
45		49.8	162.5	1.51	2,900	89.2	96.0
47		72.4	159.0	1.52	2,700	85.0	89.0
48		48.5	163.5	1.50	2,700	83.5	93.3
49		73.5	154.0	1.50	2,350	76.2	78.3
50		54.3	149.5	1.48	2,800	93.6	94.5
50		64.2	163.0	1.69	3,550	87.0	84.0
50		61.4	160.0	1.64	3,300	103.0	100.6
52		66.8	175.0	1.81	4,100	94.0	91.0
52		73.0	171.0	1.85	3,900	91.3	84.4
52		78.0	168.0	1.86	3,900	92.8	83.8
53		63.5	176.0	1.78	4,200	95.4	94.3
53		63.8	152.0	1.61	2,800	92.1	86.9
53		60.4	153.5	1.58	2,500	81.4	79.0
53		70.0	174.0	1.84	4,400	101.1	91.6
54		38.9	161.0	1.35	2,000	62.1	74.0
54		50.2	155.5	1.46	2,300	73.9	78.7
54		78.3	155.0	1.77	2,500	64.6	56.5
55		64.8	168.5	1.74	3,000	71.2	68.9
55		62.0	163.0	1.67	3,800	93.3	91.1
55		63.3	170.0	1.73	3,300	77.6	76.0
56		73.0	164.0	1.79	3,500	85.3	78.3
56		61.2	178.0	1.62	2,400	75.9	74.0
56		60.1	166.5	1.77	3,100	93.0	87.5
56		54.7	171.5	1.76	3,400	79.2	77.2
57		55.9	143.0	1.45	2,100	73.4	72.4
58		66.9	160.0	1.70	2,700	84.3	79.4
58		74.0	164.0	1.80	3,700	90.2	82.2
59		46.3	171.0	1.39	2,200	72.8	79.1
59		58.0	157.0	1.58	2,200	70.0	69.6
60		43.6	163.0	1.43	2,200	67.4	76.9
62		41.5	162.5	1.40	2,000	61.5	71.4
62		54.5	162.0	1.60	2,200	67.9	68.7

TABLE 5—NORMALS—(Continued)

Age	Sex	Weight, Kg	Height, Cm	Surface Area Square Meters	Vital Capacity C c	Vital Capacity Percentage Height	Vital Capacity Percentage Surface Area
63	♂	58.6	161.0	1.61	3,400	84.5	84.1
63		80.0	173.0	1.94	3,600	83.3	74.2
63		52.8	157.5	1.51	1,500	47.6	49.6
64		57.0	167.0	1.57	1,800	43.1	45.9
64		61.3	162.0	1.65	2,100	61.7	63.1
64		58.1	173.5	1.71	3,000	69.1	70.2
65		76.6	170.0	1.88	4,150	97.6	88.3
65		59.4	150.5	1.54	2,200	73.0	71.4
66		63.1	164.0	1.68	3,600	87.8	85.7
67		52.0	166.0	1.56	3,950	95.1	101.2
68		77.7	159.0	1.80	2,350	59.1	52.2
69		72.0	167.0	1.80	3,600	86.0	79.0
70		76.0	177.5	1.94	4,300	96.8	83.6
70		57.2	157.0	1.56	2,800	71.4	71.8
70		57.7	146.5	1.50	1,700	58.0	56.6
71		54.0	164.0	1.58	2,900	70.7	73.4
72		55.5	149.5	1.49	1,700	56.8	57.0
72		68.1	161.0	1.72	1,300	32.3	30.2
72		70.4	156.5	1.71	2,200	70.2	64.0
73		81.0	170.0	1.93	2,400	56.4	49.8
73		65.0	161.0	1.68	2,500	62.1	59.3
74		41.1	157.0	1.36	2,300	73.2	84.5
75		57.3	157.0	1.57	2,150	68.4	68.4
75		47.2	150.0	1.40	1,300	43.3	46.4
75		61.3	169.0	1.70	3,600	85.3	84.5
75		69.0	170.0	1.8	2,600	61.1	57.7
75		68.6	157.0	1.7	2,100	53.5	49.4
76		56.8	160.0	1.58	1,700	53.1	53.8
79		75.0	171.0	1.87	2,900	67.9	62.0
81		73.1	163.0	1.79	2,350	57.7	52.5
82		41.5	155.0	1.35	1,000	32.2	31.0
84		58.1	160.0	1.60	2,650	66.0	66.0
84		64.5	154.0	1.62	1,100	35.7	33.8
85		51.3	149.5	1.44	1,400	46.8	48.6
86		35.4	141.0	1.18	1,200	42.5	50.8
94		56.8	158.5	1.57	2,200	69.4	70.0

TABLE 6—OVERWEIGHTS

Age	Sex	Weight, Kg	Height, Cm	Surface Area Square Meters	Vital Capacity C c	Vital Capacity Percentage Height	Vital Capacity Percentage Surface Area
48	♂	96.6	175.0	2.13	4,100	93.0	77.0
45		89.0	172.0	2.03	5,000	116.2	98.6
48		79.8	156.5	1.80	2,250	71.8	62.5
56		79.0	158.0	1.80	2,200	69.6	60.9
60		78.8	171.0	1.91	2,900	85.0	76.0
53		78.8	164.0	1.86	3,225	98.0	87.0
29		78.5	164.0	1.85	3,000	91.0	80.0
41		78.0	158.5	1.80	2,000	63.0	55.5
39		77.0	163.5	1.83	2,900	71.0	63.0
59		76.3	153.5	1.74	2,100	68.0	60.0
24		75.7	165.0	1.83	3,020	92.0	83.0
42		75.5	157.7	1.77	2,550	80.8	72.0
51		75.5	165.5	1.83	2,300	69.4	62.8
33		75.2	159.5	1.67	2,750	86.8	82.0
21		73.8	156.0	1.74	2,750	88.1	79.0
52		73.6	152.0	1.71	2,300	75.8	67.2
38		71.7	154.0	1.71	3,000	97.0	87.7
54		71.6	162.0	1.76	2,300	70.9	65.3
23		71.5	152.0	1.68	2,800	92.1	83.3
58		71.2	159.5	1.74	2,900	72.6	66.6
40		66.1	152.0	1.63	2,450	80.5	75.1
29		64.7	157.0	1.64	1,700	54.0	52.0
21		64.0	157.6	1.65	2,800	88.8	84.8



purpose of observing the effect on symptoms and vital capacity. The reduction in all exceeded 10 kg and was brought about in periods, varying from two to ten months. Dyspnea was present in three, and general symptoms, easy fatigue, lassitude and a "heavy feeling" was complained of by all. The vital capacity was above 100 per cent in but one case, the subject being the only one of the four who did not have dyspnea. These symptoms improved or disappeared in all coincident with the loss of weight. The vital capacity in cubic centimeters increased in two cases, but remained constant in the others. In one

TABLE 7—OBESITIES

Age	Sex	Weight kg	Height, Cm	Surface Area Square Meters	Vital Capacity Cc	Vital Capacity Percentage Height	Vital Capacity Percentage Surface Area
33	♀	108.2	171.0	2.82	3,000	87.7	53.0
34	♀	129.5	153.0	2.18	2,400	78.0	55.0
20	♀	114.9	164.5	2.17	2,700	82.2	61.9
33	♀	114.0	162.0	2.15	3,000	93.0	70.0
53	♀	112.3	169.5	2.20	3,400	80.0	62.0
50	♀	112.2	159.0	2.10	2,900	73.0	55.1
63	♀	106.66	164.0	2.12	2,500	76.6	59.0
42	♀	107.9	157.5	2.04	2,200	70.0	54.0
63	♀	104.4	165.0	2.11	2,500	60.6	47.4
40	♀	98.2	159.0	2.00	2,900	91.0	72.5
42	♀	94.1	154.0	1.92	2,450	79.5	63.8
45	♀	91.7	162.2	1.97	2,700	83.0	68.5
21	♀	88.8	164.5	1.96	3,100	94.2	79.0
42	♀	87.2	164.0	1.94	3,500	85.3	72.1
47	♀	86.8	173.5	2.02	3,300	95.0	82.0
26	♀	86.4	159.0	1.89	3,350	105.0	89.0
48	♀	86.0	168.0	1.96	2,850	84.8	72.7
54	♀	84.7	166.5	1.94	2,600	62.5	53.5
31	♀	84.7	162.0	1.90	3,730	115.0	93.0
32	♀	83.9	153.0	1.85	3,000	94.3	81.0
50	♀	83.3	158.0	1.85	2,100	66.4	56.7
55	♀	82.4	163.0	1.88	2,100	64.0	55.0
22	♀	82.2	173.0	1.79	2,600	84.9	72.6
35	♀	80.6	165.5	1.88	3,000	91.0	80.0
52	♀	80.0	156.0	1.80	2,300	74.0	64.0
26	♀	79.4	150.0	1.79	3,250	104.0	90.7
52	♀	78.3	148.5	1.71	2,000	67.0	58.0
34	♀	77.1	152.5	1.74	2,200	72.1	63.2
50	♀	77.0	133.0	1.74	2,700	88.2	77.5
40	♀	74.2	167.5	1.83	3,200	95.5	87.5
43	♀	74.8	154.5	1.74	2,400	77.6	68.9
23	♀	73.9	150.5	1.68	2,800	93.0	83.0

of these the increase was 27.5 per cent by height. While this is interesting, it is not consistent with the findings in the other cases. However, in these four cases, after the weight reduction there was an increase in the vital capacity by surface area, bringing it nearly to normal. This study would indicate that the tendency to dyspnea which is common in people who are overweight is possibly, in part, accounted for by a reduction in vital capacity. Presumably, it is wise to reduce the weight of overweight persons slowly, if they complain of symptoms suggesting cardiac embarrassment. This is especially so if their vital capacity shows a definite reduction.

## CONCLUSION

This study seems to warrant the following deductions

1 Using standards based on persons between the ages of 20 and 30, the vital capacity is within normal limits up to the age of 50, thereafter the fall is gradual, reaching 50 per cent at the age of 85. The greatest drop is between the ages of 50 and 60.

2 The vital capacity of obese and "overweight" people is but slightly less than normal, using the height standard, but averages 20 per cent less by surface area, up to the age of 50.

3 The height standard, or the addition of 20 per cent to the result obtained by using the surface area standard may be used in estimating the vital capacity of obese or "overweight" subjects.

4 The tendency to dyspnea, which is often present in people who are much overweight, may be accounted for, in part, by a reduction of the vital capacity.

5 It appears advisable to reduce the weight of obese people slowly, if there are annoying symptoms of a cardiac nature. This is especially so if the vital capacity shows a definite reduction.

# ACID-BASE EQUILIBRIUM

## I CLINICAL STUDIES IN ALKALOSIS \*

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Although the practical aspects of the acid-base equilibrium problem are appreciated by the clinician, the observations and discussions have been limited to a large degree to those cases in which the equilibrium has been shifted toward the acid side. Observations reported in the last few years and our own studies indicate that an alkalotic condition of the body is perhaps as important clinically, if not more so, than an acidotic condition. In an acidosis resulting from the ingestion of fixed acids, from the retention of carbon dioxide, from deficient oxidation with the resulting accumulation of acid metabolites, or by acid retention due to renal involvement, there is at first an increased lung ventilation, but only after a decided acidosis of  $p_H$  7.1—7.0 is there a marked disturbance of the normal physiological functions characterized by unsteadiness of motion, stupor and a coma, usually passing into death.

In order to clarify the discussion it is well to recall the possible variations in the acid-base balance as presented recently by various writers in a greatly clarified manner. The fundamental conception which displaced the chaos and confusion of this problem with a practical working knowledge was set forth by Hasselbach<sup>1</sup>. He showed that in blood there was a definite relationship among three interdependent variables,  $\text{NaHCO}_3$ ,  $\text{CO}_2$  and  $p_H$ , so that the determination of any two would give the third:

$$p_H = K \frac{\text{H}_2\text{CO}_3}{\text{NaHCO}_3}$$

When the reaction of the blood is normal,  $p_H = 7.4$ , the ratio of  $\text{H}_2\text{CO}_3$  to  $\text{NaHCO}_3$  is as 1 is to 20 or

$$\frac{0.00155 \text{ mol per liter H}_2\text{CO}_3}{0.0310 \text{ mol per liter NaHCO}_3} = \frac{1}{20} \text{ equiv to } p_H = 7.4$$

The mathematical relationship Hasselbach gave as follows:

$$p_H = pK_1 + \log \frac{\text{NaHCO}_3}{\text{H}_2\text{CO}_3}$$

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\* From the Laboratory of Physiological Chemistry, University of Wisconsin.  
 1 Hasselbach, K. A. Die "reduzierte" und die "regulierte" Wasserstoffzahl des Blutes, *Biochem. Ztschr.* 74: 56, 1916.

The value of  $pK_1$  was shown by Haggard and Henderson<sup>2</sup> to be 6.10. An example for normal blood would be

$$6.10 + \log \frac{50 \text{ (vol \% CO}_2 \text{ as NaHCO}_3\text{)}}{25 \text{ (vol \% CO}_2 \text{ as H}_2\text{CO}_3\text{)}} = p_H = 7.4$$

However, it has been more recently shown by L. J. Henderson<sup>3</sup> that the above interdependence of the three variables,  $p_H$ ,  $\text{NaHCO}_3$ , and  $\text{H}_2\text{CO}_3$  extends also to three more important simultaneous variables, namely free oxygen ( $\text{HbO}_2$ ) and the chlorid content of the plasma ( $\text{PCl}$ ). This may also be presented as follows

$$\frac{\text{HCO}_3}{\text{NaHCO}_3} = K \frac{\text{O}_2}{\text{HbO}_2} = K \frac{p_H}{\text{PCl}}$$

The above conception is indeed a very helpful simplification of the heretofore indefinite notions of the relation of the blood buffers. It is also altogether probable that this interdependence applies not only to the respiratory variables but that a mathematical expression can be formulated including all the buffer systems of the blood, as for example

$$p_H = K \frac{\text{NH}_2\text{PO}_4}{\text{N}_2\text{HPO}_4} = K \frac{\text{Acid Proteinate}}{\text{Protein}} = K \frac{\text{Protein}}{\text{Na Proteinate}} \text{ etc}$$

It is, therefore, apparent that in clinical studies we are only concerned with the determination of two variables in order to define our systems. Up to the present time these variables have been either  $p_H$  and  $\text{NaHCO}_3$  or  $\text{H}_2\text{CO}_3$  as  $\text{CO}_2$  tension and  $\text{NaHCO}_3$ . D. D. Van Slyke<sup>4</sup> has given a very clear presentation based on the above three variables of the possible variations in acid-base balance. He sets forth nine possible conditions, all of which may occur clinically. The bicarbonate may be high, low or normal and in each condition the  $p_H$  may be high, low or normal. A helpful terminology has been introduced in which abnormal bicarbonate variations with a normal  $p_H$  are spoken of as compensated and bicarbonate variations with abnormal  $p_H$  as uncompensated alkalosis or acidosis. There thus occurs a condition of compensated alkali or carbon dioxide excess, which condition may pass either to uncompensated alkali excess with a high  $p_H$ , 7.5-7.8, or to uncompensated carbon dioxide excess with a low  $p_H$ , 7.3-7.0. Similarly a compensated alkali or carbon dioxide

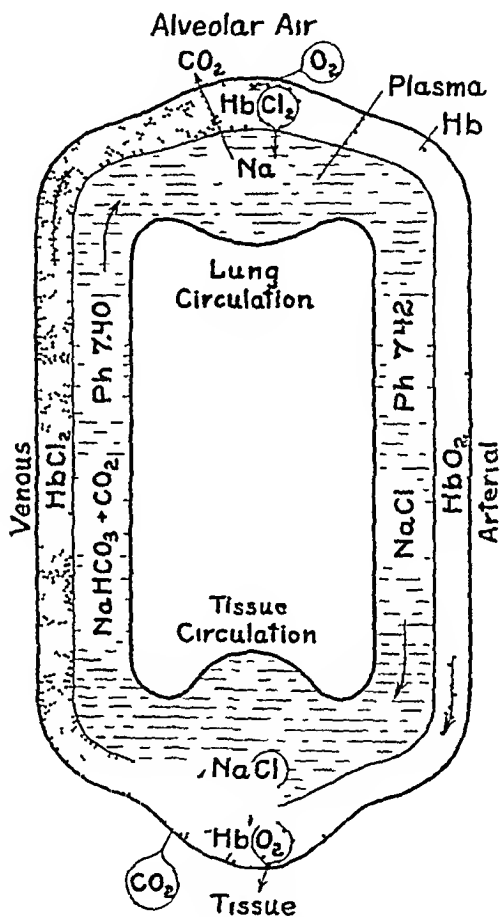
<sup>2</sup> Haggard, W. H., and Henderson, Y. Hematorespiratory Functions, *J Biol Chem* **39** 163, 1919.

<sup>3</sup> Henderson, L. J. Blood as a Physicochemical System, *J Biol Chem* **46** 411, 1921.

<sup>4</sup> Van Slyke, D. D. Studies of Acidosis, XVII. The Normal and Abnormal Variations in the Acid-Base Balance of the Blood, *J Biol Chem* **48** 153, 1921.

deficit may pass either to uncompensated alkali deficit with a  $p_H$  of 7.3-7.0 or to uncompensated carbon dioxide deficit with a  $p_H$  of 7.5-7.8

In order to understand the relationship of the changes within the blood to the acid-base balance and oxygen exchange of the body, it will be necessary to consider more closely the changes that occur in the variables  $p_H$ ,  $\text{NaHCO}_3$ ,  $\text{H}_2\text{CO}_3$ ,  $\text{O}_2$ ,  $\text{HbO}_2$  and plasma chlorid as represented by the L. Henderson<sup>4</sup> nomogram during the normal circulation of the blood. These changes can best be understood from a study of the diagram. This diagram shows in a qualitative way the



Blood changes in a respiratory cycle

blood changes in a respiratory cycle. The top portion represents the lung capillary circulation and the bottom portion represents the tissue circulation. The whole blood represented by the enclosed system is divided diagrammatically into plasma and red corpuscles or hemoglobin, thus making it possible to indicate the changes that take place between them. A convenient place to start to follow the changes indicated in the cycle is in the tissue capillary circulation. The carbon dioxide produced in the tissues passes to the plasma, where the carbon dioxide

tension is lower. The dissociation of the sodium chlorid renders the sodium ion available for the formation of sodium bicarbonate with the carbon dioxid. The passage of the chlorin ion to the  $\text{HbO}_2$ , together with the change in oxygen tension, is instrumental in the passage of the oxygen to the tissues, leaving  $\text{HbCl}$ . The venous blood now carries a large amount of  $\text{H}_2\text{CO}_3$  and  $\text{NaHCO}_3$  in such a ratio that it has but a slightly lower  $p_{\text{H}}$  than that of arterial blood. The hemoglobin, which has been instrumental in carrying oxygen, is now returned as the chlorid. When the venous blood reaches the pulmonary circulation the reverse processes take place. The carbon dioxid is given up to the lower gaseous tension of the alveolar air, thus liberating the sodium. This would, however, leave the plasma too alkaline, so the chlorin passes from the hemoglobin to the plasma to again form sodium chlorid. This change, together with reversed change in oxygen tension, enables the oxygen to pass from the alveoli to the hemoglobin. The arterial blood then carries  $\text{HbO}_2$  and the chlorin as sodium chlorid ready to repeat the cycle. It must, however, be remembered that this is merely a schematic representation of a few of the variables of a very complex system and that the reason for the changes and their exact mechanism of action is very imperfectly understood.

Two methods have been used for accurate determinations of acid-base variations in whole blood. In this laboratory we use the gas chain method for determining the  $p_{\text{H}}$  and the Van Slyke apparatus for determining the total carbon dioxid. Haggard and Henderson<sup>2</sup> have introduced a method by means of which the  $p_{\text{H}}$  can be measured indirectly by equilibrating blood with various known carbon dioxid tensions and then determining the combined carbon dioxid for each tension. In this way, by plotting the total carbon dioxid against carbon dioxid tension a  $p_{\text{H}}$  line is determined. The practicability of this method is as yet questionable, inasmuch as it introduces a third variable—a change of the oxygen tension of the blood. The exact effect of this is as yet not clear.

#### CLINICAL ALKALOSIS

Clinically alkalosis falls either into alkali excess or carbon dioxid deficit. In either case the  $p_{\text{H}}$  is above normal and is usually within the limits of  $p_{\text{H}}$  7.5-7.8. Alkali excess is usually the result of excessive administration of sodium bicarbonate either by mouth or intravenously.<sup>5</sup>

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<sup>5</sup> Howland, J., and Marriott, W. McK. Observations on the Calcium Content of the Blood in Infantile Tetany and on the Effect of Treatment by Calcium, *Quart. J. M.* **11** 289, 1917.

We have observed it as the result of prolonged administration of sodium citrate, sodium acetate and sodium bicarbonate, together with sodium salicylate in rheumatic fever. Alkali excess also obtains in loss of hydrochloric acid from the stomach in pernicious vomiting or in pyloric obstruction with subsequent vomiting or washing out the stomach for several days with a stomach pump.<sup>6</sup>

In uncompensated carbon dioxide deficit the  $p_{\text{H}}$  is above the normal limits, thus designating an alkalosis, although there really is a marked diminution in blood and body alkali. This reduction of alkali is the result of a tendency of the body to reduce the alkali to such a level that it will compensate the low carbon dioxide level. This condition can be caused by voluntary hyperpnea.<sup>7</sup> It also obtains in anoxemic dyspnea either as a result of decreased oxygen supply<sup>8</sup> or in failure of the blood to carry oxygen as in the early hours of carbon monoxide poisoning.<sup>9</sup> It has also been shown to exist in the elevation of body temperature by immersion in warm water.<sup>10</sup>

The effects of either alkali excess or carbon dioxide deficit to a large extent are the same. Unless there is an accompanying renal involvement, the urine tends to become alkaline owing to elimination of alkali. In alkali excess the bicarbonate elimination is very much greater, often several grams per hour, than in carbon dioxide deficit where the excretion usually is only a fraction of a gram per hour.<sup>11</sup> In either case there is a diminution of titratable acids with a comparable decrease or even complete absence of ammonia. The elimination of acetone bodies has also been noted under both conditions.<sup>11</sup> A point of difference however, is the increase in alveolar carbon dioxide in alkali excess and a decrease in carbon dioxide deficit.

The outstanding clinical symptoms of a marked alkalosis of either type have been well described by various writers as the characteristic

6 MacCallum, W. A., Luntz, J., Vermilye, H. N., Leggett, T. H., and Boas, E. The Effect of Pyloric Obstruction in Relation to Gastric Tetany, *Bull. Johns Hopkins, Hosp.* **31** 1, 1920.

7 Collip, J. B., and Backus, P. L. The Effect of Prolonged Hyperpnea on the Carbon Dioxide Combining Power of the Plasma, the Carbon Dioxide Tension of Alveolar Air, and the Excretion of Acid and Basic Phosphate and Ammonia by the Kidney, *Am. J. Physiol.* **51** 568, 1920.

8 Haggard, W. H., and Henderson, Y. Hematorespiratory Functions. The Fallacy of Asphyxial Acidosis, *J. Biol. Chem.* **43** 3, 1920.

9 Haggard, W. H., and Henderson, Y. Hematorespiratory Functions. Respiratory and Blood Alkalinity during Carbon Monoxide Asphyxia, *J. Biol. Chem.* **47** 421, 1921.

10 Haggard, W. H., Bazett, H. C., and Haldane, J. B. S. Hematorespiratory Functions. The Alteration of the Carbon Dioxide Ratio in the Blood during Elevation of Body Temperature, *J. Biol. Chem.* **44** 131, 1920. Some Effects of Hot Baths on Man, *J. Physiol.* **55**, IV, 1921.

11 Davies, H. W., Haldane, J. B. S., and Kennaway, E. L. Experiments on the Regulation of the Blood's Alkalinity, *J. Physiol.* **54** 32, 1920.

development of tetany and, finally, convulsions<sup>6, 12</sup> The various steps in the development of tetany are best seen in marked voluntary hyperpnea The picture is practically identical with that seen at the bedside in severe alkalosis There is at first noted a numbness of the extremities especially the fingers This is followed by a tingling of the fingers, quivering of the eyelids and a tenseness of the facial muscles The fingers become flexed at the metacarpophalangeal joints in a characteristic manner and may suddenly go into a marked spasm The facial muscles go into a decided quiver with most marked contraction of the orbicularis oris, risorius and triangularis muscles, giving rise to a peculiar grinning expression and difficulty of articulation Tapping a branch of the facial nerve, Chvostek's sign for tetany, results in spasmodic contraction of the facial muscles

Erb's sign of increased electrical irritability of the muscles of the forearm is apparently a constant accompaniment of a high blood  $p_H$  Trousseau's sign is also of diagnostic value in the determination of the onset of the tetany of alkalosis

As to the causative relation of alkalosis to tetany little is known beyond a few general observations Biederman<sup>13</sup> showed that the excitability of isolated voluntary muscle was greatly heightened by increasing, up to a certain limit, the alkalinity of the solution in which it was immersed Dale and Thacker<sup>14</sup> demonstrated decreased duration of the sino-auricular interval, the auriculoventricular interval and the cardiac cycle with increase in hydroxyl ions in perfusion of the frog's heart McClendon obtained similar results in studying the effect of reaction on the pulsation rate of the hearts of the jelly fish and conch That alkalotic tetany is the result of change in the muscle or myoneural junction rather than in the nerve fiber proper may be interpreted from the work of Adrian<sup>15</sup> who demonstrated the disappearance of the supernormal phase of a nerve-muscle preparation on the alkaline side of  $p_H$  7.4 when the nerve fiber was submerged in a buffered Ringer's solution He found that this decrease on the alkaline side holds good for the recovery of conductivity as well as that of excitability

As yet there is no good evidence that calcium, with its bearing on idiopathic and parathyroid deficiency tetany, has any relationship to alkalotic tetany Although improvement of the tetanic symptoms can

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12 Grant, S. B., and Goldman, A. A Study of Forced Respiration Experimental Production of Tetany, *Am J Physiol* **52** 209, 1920

13 Biederman *Electrophysiology*, New York, 1898, p. 104

14 Dale, D., and Thacker, C. R. Hydrogen Ion Concentration Limiting Automaticity in Different Regions of the Frog's Heart, *J Physiol* **47** 493, 1914

15 Adrian, E. D. The Recovery Process of Excitable Tissues, *J Physiol* **54** 1, 1920



be noted in some cases on administration of a soluble calcium salt,<sup>4</sup> the results do not always run favorably and improvement can, perhaps, be attributed to the well known sedative action that calcium has in reducing the excitability of the nervous system. That serum calcium is low in infantile tetany is shown in a mass of analytical data presented by Howland and Marriott,<sup>5</sup> and recent work by Hastings and Murray<sup>16</sup> shows a similar drop in the tetany following parathyroidectomy. It is as yet an open question as to the condition of the acid-base equilibrium in these diseases. It can, however, be stated with reasonable assurance that all tetanias are not alkalotic as to origin.

With the foregoing brief survey of our present knowledge of alkalosis it was thought desirable to investigate various conditions which occur clinically as possibly related to alkalosis.

#### METHODS

The blood samples were drawn from the median basilic vein of the arm (unless otherwise stated). A tube containing heavy paraffin oil and a small amount of dry potassium oxalate similar to the one described by Van Slyke<sup>17</sup> was used. A 21 gage needle was used to insure the quick flow of blood. In order to obtain the sample quickly a tourniquet was used at times to insert the needle. Determinations were usually made within one half hour after the sample was obtained.

*Determination of Total Carbon Dioxid*—The total carbon dioxide was determined directly, using the Van Slyke apparatus on whole blood without equilibrating. One half c.c. 20 per cent tartaric acid was found even better than normal lactic acid which Van Slyke and Stadie<sup>18</sup> had substituted for normal sulphuric acid when using whole blood. The tartaric acid dissolves the blood proteins completely so that the apparatus can be washed clean after each determination.

The hydrogen ion concentration was determined on whole blood by means of the hydrogen electrode. The electrode vessel was of the McClendon pattern but modified so that the platinum electrode could be removed as in the Clark electrode design. A tenth normal calomel electrode and connecting bridge, as previously described,<sup>19</sup> was used.

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16 Hastings, A. B., and Murray, H. A. Observations on Parathyroidectomized Dogs, *J Biol Chem* **46** 233, 1921.

17 Van Slyke, D. D. Studies of Acidosis, I. The Bicarbonate Concentration of the Blood Plasma, Its Significance, and Its Determination as a Measure of Acidosis *J Biol Chem* **30** 289, 1917.

18 Van Slyke, D. D., and Stadie, W. C. The Determination of the Gases of the Blood, *J Biol Chem* **49** 1, 1921.

19 Kochler, A. E. A New Tenth Normal Calomel Electrode Design, *J Biol Chem* **41** 619, 1920.

The rocking electrode, connecting bridge and calomel electrode together with the washout vessels and Weston standard cell were enclosed in a constant temperature air bath similar in design to that described by Clark<sup>20</sup> but being constructed of double glass walls with an air tight dead space in between. The temperature for all determinations was 25 C. The hydrogen which was generated electrolytically was washed over concentrated sulphuric acid and ignited by means of heated platinized asbestos. The hydrogen was saturated with water at 25 C by bubbling through wash bottles set within the air bath. A Leeds and Northrup type K potentiometer was used for the potential measurement.

## EXPERIMENTAL

*The Blood Reaction in Acute Fevers*—All the cases studied were those of students confined at the university infirmary. Nearly all the cases were those of a grippe-like infection with a moderately high fever during the first and sometimes the second day after entrance and a return to normal in three or four days. Dover's powders, 5 grains, acetphenetidin, 2 grains and acetylsalicylic acid, 2 grains, had been given in most cases shortly after entrance, at three hour intervals. In the majority of cases loss of appetite resulted in a very low intake of food, often only water having been taken for the preceding twenty-four hours.

TABLE 1—BLOOD REACTION IN ACUTE FEVERS

Case	Day of Sample*	Temperature	Respiration	Pulse	P <sub>n</sub>	Total CO <sub>2</sub>	Remarks
1	2	103.4			7.513	48.3	Grippe
	5	98.0			7.394	46.6	
2	1	104.0			7.561	46.6	Grippe (no food)
	4	98.0			7.431	30.5	
3	3	103.6	24	104	7.516	41.4	Bronchopneumonia
	7	98.7	15	65	7.440	57.5	
4	1	101.2			7.459	49.8	Carbuncle on neck
	2	98.4			7.410	50.3	
5	3	103.2			7.530	47.5	Grippe
	5	98.7			7.411	52.6	
6	4	103.0	20	100	7.600	46.6	Influenza (cyanotic)
	8	98.6	14	70	7.412	54.6	
7	1	103.0	21	108	7.562	45.0	Grippe (cyanotic)
	6	98.0			7.423	53.8	
8	3	103.6	24	116	7.501	49.1	Grippe
	5	98.4	14	74	7.421	52.8	
9	2	103.7	27	110	7.557	41.8	Grippe
	4	97.9	16	72	7.413	51.7	
10	2	103.8	26	112	7.533	44.9	Grippe
	5	98.1	14	68	7.409	51.8	
11	1	103.0	23	109	7.511	48.0	Grippe
	4	98.2	15	71	7.431	52.2	
12	2	102.8	24	108	7.468	44.7	Grippe
	3	97.8	14	69	7.347	47.1	
13	1	101.6	20	105	7.451	44.8	Grippe
	3	98.0	14	73	7.423	49.0	
14	4	103.0			7.438	48.5	Influenza, alveolar abscess
	8	97.8			7.428	55.6	
15	4	102.2	26	114	7.431	44.5	Peritonitis, fatal
	5	105.0†	27	116	7.362	44.6	sixth day

\* Day after onset of illness

† Rectal

Of twelve cases studied with a temperature of 103 F or over, ten showed an uncompensated alkalosis. In the other two cases, one patient (Case 14), suffering from hypopituitarism, severely ill with influenza of four days' duration and suffering from an alveolar abscess, showed a  $p_H$  of 7.438, the other (Case 15), a student very ill from a peritonitis and septicemia, showed on the fourth day, 102.2 F (axillary), a  $p_H$  of 7.431, and on the fifth day, 105.0 F (rectal),  $p_H$  of 7.362, the sixth day being fatal. In both cases the food intake was practically nil during the period of severe illness.

In three cases with a temperature of from 101 to 102.8 F, the condition was that of compensated alkalosis.

All cases, except one, showed a drop in fixed carbon dioxide with a return to normal both of fixed carbon dioxide and  $p_H$ , on recovery. In one case (Case 2), food was withheld, except in very small quantities, for several days on account of abdominal pains and a suspected peritonitis with the resultant failure of the alkali to return to normal even though the  $p_H$  had recovered.

TABLE 2—EFFECT OF STARVATION ON BLOOD REACTION

Subject	Normal		50 Hours		77 Hours		Remarks
	$p_H$	Volume per Cent Total CO <sub>2</sub>	$p_H$	Volume per Cent Total CO <sub>2</sub>	$p_H$	Volume per Cent Total CO <sub>2</sub>	
C P C	7.448	55.0	7.404	41.3	7.365	38.0	Complete rest
E B P	7.501	58.6	7.466	48.0	7.381	43.1	Complete rest
A E K	7.437	54.0	7.401	43.0	7.302	36.0	Daily work

Since most of these subjects underwent a period of starvation during high fever, a study was made on the effect of short periods of starvation on normal persons.

*Effect of Starvation on Blood Reaction*—Three subjects were observed, all in good physical condition. Two were confined to complete rest in bed at the infirmary; permitted to do light reading only. The third subject, fasting for the same period, walked to and from work, a distance of several miles, and carried on a normal laboratory routine during the day.

Although the development of an acidosis on starvation has been looked on as a fact for many years, measurements of the actual blood changes have been lacking. The figures in Table 2 show that even in short periods of starvation there is a definite change in  $p_H$  toward the acid side. In all probability this drop in  $p_H$  is due to the constant elimination without replenishing of body alkali with endogenous acids, such as phosphoric and sulphuric, from protein catabolism. In a seventy-seven hour period this drop of alkali still is compensated by a

drop in carbon dioxid tension of the body fluids but a condition of uncompensated acidosis, especially in a subject not at rest, is approached

The relation that this tendency toward an acidosis during short periods of starvation even at complete rest bears upon the observations during fever is important inasmuch as the changes are in the opposite direction, thus augmenting the difference. This tendency is perhaps a factor in "starve a fever" rationale

To show whether or not the increase of blood  $p_H$  during an acute fever is due to the elevation of the body temperature per se or, perhaps, is due directly, or, in part, to the infection,  $p_H$  and total carbon dioxid measurements were made on subjects whose body temperature was increased by submersion in warm water

Subject 1 experienced tingling sensation of fingers, numbness of extremities with pin prick anesthesia, saw concentric circles before the eyes at fifteen minutes, suffered mental confusion, marked quivering of eyelids when attempting to open, was unable to raise eyelids, because of

TABLE 3—EFFECT OF SUBMERSION IN WARM WATER ON BLOOD REACTION

	Water Temper- ature, C	Oral Temper- ature, F	$P_H$	Total CO <sub>2</sub>	Mm CO <sub>2</sub> Tension	Pulse	Respi- ration
Subject 1							
0 Min	41	98	7.390	58.4	47.0	78	15
15 Min	42.5	102.4	7.567	42.7	24.0	115	24
30 Min	43.4	103.2	7.605	38.1	20.1	132	29
Subject 2							
0 Min	41.5	98.4	7.420	51.8	41.0	76	16
15 Min	44.8	103.8	7.521	45.4	28.0	132	24
20 Min	45	103.3	7.365	50.9	43.0	120	27
Subject 3							
0 Min	42.0	97.8	7.479	53.1	42.0	60	14
23 Min	44.0	104.3	7.563	42.2	28.5	128	20
37 Min	44.3	104.6	7.441	47.5	35.0	130	24

tetanic contraction of the rectus abdominis muscle, and was unable to straighten and unable to use limbs

Subject 2 breathed from 8 to 10 per cent carbon dioxid during the period from 15 to 20 minutes. The man felt weak and generally distressed, with no marked signs or symptoms. He said carbon dioxid made him feel very much better, and he got up and walked out of the tub, with quick recovery.

Subject 3 breathed carbon dioxid during the 5 minute period from 32 to 37 minutes. He felt dizzy, and very weak, had tingling of the fingers, mental confusion, numbness of extremities, flexion of wrist and metacarpophalangeal joints. He felt much better after a 15 minute period, said carbon dioxid made him feel very much better.

The acid-base balance of the blood and the various signs and symptoms of the subjects, either in natural or hot water fever, offer a picture very similar to that already discussed under forced dyspnea. In order to show this relation more clearly, a few experiments taken

from a paper soon to be published will be helpful <sup>20a</sup> Medical students in good physical condition were studied in respect to normal volume respiration, normal oxygen consumption, normal carbon dioxid output, and again with respect to total carbon dioxid washed out from the whole body and the drop in total carbon dioxid per c c of blood after forced hyperpnea The "Benedict Universal" metabolism apparatus was used for the determinations

*Voluntary Hyperpnea*—These subjects developed the characteristic tetanic symptoms as described by Grant and Goldman <sup>12</sup>

That a similar hyperpnea with a corresponding picture of changes can be produced by a warm water fever is shown by the following experiment, similar to the first, except that in place of voluntary hyperpnea the subject was immersed in warm water and an otherwise normal resting metabolism rate measurement was made

TABLE 4—ACID-BASE BALANCE OF NORMAL SUBJECTS

	Subject	Normal, 10 Minute Period	Hyperpnea 10 Minute Period	Difference
Volume respiration c c	C H	80,923	235,834	154,931
	R S	59,739	251,248	191,509
O <sub>2</sub> consumption, c c	C H	3 150	5,065	1,915
	R S	2,485	5,390	2 905
CO <sub>2</sub> output c c	C H	2 891	5,909	3,018
	R S	2,158	5,507 3	3,349
Blood total CO <sub>2</sub> volume per cent	C H	55 9	49 7	0 620
	R S	59 6	51 2	0 840
Pn	C H	7 460	7 605	0 145
	R S	7 451	7 657	0 206

FEVER DISCUSSION

Various investigators have from time to time dwelt on the development of an acidosis during fever until this view has become generally accepted A careful examination of the observations on which the acidotic view has been based in the light of our present knowledge of the acid-base balance does not necessarily indicate an acidosis nor even an acidotic tendency

The fact that the alveolar carbon dioxid tension is reduced during thermic fever, as first shown by Hill and Flack <sup>21</sup> has been looked on as confirming the acidotic view <sup>22</sup> It will be remembered, however,

20 a—Work carried on in cooperation with Dr F J Hodges, Department of Physiology, University of Wisconsin

21 Hill, L, and Flock, M The Influence of Hot Baths on Pulse Frequency Blood Pressure Body Temperature, Breathing Volume, and Alveolar Tensions of Man, J Physiol 38 p lvi, 1909

22 Barbour, H G Heat Regulating Mechanism of the Body, Physiol Rev 1 305 1921

that reduced carbon dioxid tension of the alveoli or blood alone may be diagnostic of either an acidosis or an alkalosis—the latter of the carbon dioxid deficit type as produced by hyperpnea

Increased metabolism of the animal body during a rise in temperature has often been associated with an acidosis. Increased nitrogen elimination has been attributed to an increase in the autolytic processes due to increased H ion concentration. Mansfeld and Ernst<sup>23</sup> ascribe the increased protein destruction in fevers to the thyroid gland with its well known control over body oxidation. Recently, however, Du Bois,<sup>24</sup> in studying the basal metabolism in fever, has shown that the rate of oxidation in the animal body is directly proportional to the rise in temperature according to the temperature law of van't Hoff. Thus for every 10 degrees rise in temperature the rate of oxidation is increased approximately 2.5 times. He has shown that the basal metabolism of a fever patient is 13 per cent higher for each degree Centigrade above normal.

TABLE 5—EXPERIMENTAL HYPERPNEA IN A NORMAL SUBJECT PRODUCED BY SUBMERSION IN WARM WATER

	Water Temper- ature, C	Oral Temper- ature, F	Volume Respi- ration per Min C c	O <sub>2</sub> Con- sumption 5 Min per C c	CO <sub>2</sub> output 5 Min per C c	Blood Total CO <sub>2</sub> Volume per Cent	P <sub>H</sub>	Pulse	Respi- ration per Min
0 Min	42.1	98.2	6,165	1,176	906	52.3	7.432	68	10.6
23 Min	43.8	103.1	19,542	2,317	1,603	42.5	7.521	128	19-21
37 Min	44.0	103.8						130	20-24

The excretion of acetone bodies during a fever does not necessarily mean an acidosis as acetone bodies have been observed in induced alkalosis, both in the alkali excess and carbon dioxid deficit types.<sup>11</sup> In fact, Bazett and Haldane<sup>25</sup> noted the excretion of acetone bodies during hot baths with all the indications of an alkalosis—diminished fall in alveolar carbon dioxid, markedly alkaline urine with high bicarbonate and no ammonia elimination.

Thus, it is readily seen that if the various experiments leading to the acidotic conception are examined for definite information as to exact measurements for an acidosis, it is, to our knowledge, not obtainable.

Haggard<sup>10</sup> was the first to obtain direct measurements of blood changes during immersion in hot water which enabled him to foretell

23 Mansfeld, G., and Ernst, G. Ueber die Ursache der gesteigerten Eiweisszersetzung und Warmebildung im infektiösen Fieber, *Arch f d ges Physiol* **159** 399, 1915.

24 Du Bois, E. F. The Basal Metabolism in Fever, *J. A. M. A.* **77** 352 (July 30) 1921.

25 Bazett, H. C., and Haldane, J. B. S. Some Effects of Hot Baths on Man, *J. Physiol* **55** 4, 1921.

a decrease in H ion concentration His conclusions were drawn from data obtained by determining the total carbon dioxide in blood and alveolar carbon dioxide or carbon dioxide tension of the blood by equilibrating with known carbon dioxide tensions After a discussion of the various mechanical factors that might be responsible for the  $p_H$  change, he concludes that the carbon dioxide ratio is reduced even more by physiologic than mechanical factors

The data presented in this paper by direct  $p_H$  measurements verify Haggard's conclusion There is a reduction in the  $H_2CO_3$ - $NaHCO_3$  ratio with a resulting increase in  $p_H$  In clinical fevers of the acute type the  $p_H$  may mount to 7.6, a value that may be concomitant with definite distress The acid-base picture obtained in acute clinical fevers is practically identical with that of pure thermic fevers or can be duplicated in voluntary hyperpnea Bazett and Haldane<sup>25</sup> report an increase in ventilation during hot bath from a normal of 6 to 27.3 liters per minute These investigators believe that the respiratory center becomes more sensitive to carbon dioxide with a rise of temperature, thus resulting in a hyperpnea Although this may be the main reason, other factors may contribute, or, in fact, offer an explanation of the foregoing mechanism With the increase in oxidation in the body from a rise in temperature, it is altogether probable that there is a definite oxygen want in the tissues, thus resulting in an anoxic stimulation of the respiration An investigation being carried out in cooperation with the department of pharmacology, the results of which are soon to be published, suggests that, in spite of a blood alkalosis, the early view of the hydrogen ion stimulation of respiration during anoxemia is a possible one This view is based on a study of the rate of transportation of carbon dioxide from cellular and intracellular fluids to the blood and upon a study of the acid-base balance during anoxemia The introduction of this item seems important in a discussion of alkalosis inasmuch as we have no evidence as yet that blood reaction is a definite criterion of the reaction of certain tissues or a group of cells

*Alkalosis and Oxygenation of the Blood*—An increase of the carbon dioxide tension of the blood has usually been looked upon as decreasing its oxygen capacity This relationship for normal whole blood was the result of the researches of Barcroft and his associates<sup>26</sup> The investigation of Christiansen, Douglas and Haldane<sup>27</sup> established the fact that the concentration of the two variables  $NaHCO_3$  and  $H_2CO_3$  determines the concentration of combined oxygen The correlation of the interdependence of these variables was shown by L. Henderson<sup>3</sup>

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<sup>26</sup> Barcroft, J. *The Respiratory Function of the Blood*, Cambridge, 1914

<sup>27</sup> Christiansen, I., Douglas, C. G., and Haldane, J. S. *The Absorption and Dissociation of Carbon Dioxide by Human Blood*, *J. Physiol.* **48**: 244, 1914

and can best be understood by a study of his nomogram. Thus, normally, an increase in carbonic acid is associated with a corresponding increase in sodium bicarbonate and  $H$  ion concentration so as to decrease the oxygenation of the blood. Conversely, a decrease in carbonic acid would result in increased oxygenation. It is, however, possible to conceive of a loss of carbonic acid decreasing the oxygen capacity of the blood. We would like to suggest this possibility as a factor in decreasing the oxygenation of the blood under pathologic conditions. Theoretically this condition could be brought about under certain conditions by an alkalosis due either to carbon dioxide deficit or alkali excess. A better understanding can perhaps be obtained by using concrete figures. The values have been taken from the nomogram of L. J. Henderson<sup>3</sup> and are only approximate.

TABLE 6—DECREASED OXYGENATION DUE TO ALKALI EXCESS

	$P_H$	$H_2CO_3$ , Mol per L	$NaHCO_3$ , Mol per L	HbO <sub>2</sub> , per Cent	O <sub>2</sub> , Mm
Normal	7.427	0.00145	0.0310	90	60
Abnormal	7.480	0.00135	0.0325	10	10

TABLE 7—DECREASED OXYGENATION DUE TO CO<sub>2</sub> DEFICIT

	$P_H$	$H_2CO_3$ , Mol per L	$NaHCO_3$ , Mol per L	HbO <sub>2</sub> , per Cent	O <sub>2</sub> , Mm
Normal	7.427	0.00145	0.0310	90	60
Abnormal	7.493	0.00125	0.0312	40	50

Several cases have come under our observation which indicate that this condition comes into play clinically.

#### FEVER CASES

Cases 6 and 7 in Table 1 were definitely cyanotic. This cyanosis was most marked when the  $p_H$  was the highest and disappeared when the acid-base balance returned to normal. Both patients were suffering from upper respiratory infection with marked constitutional reactions. It is, of course, altogether possible that with the complication of the high fever and toxemia other factors were instrumental in producing the cyanosis.

CASE 3—Female, aged 53, had a chronic myocarditis and was suffering from cerebral thrombosis. When first seen she had marked dyspnea, Cheyne-Stokes respiration at intervals, was markedly cyanotic and irrational.

A venous blood sample was taken from her forearm showing a  $p_H$  of 7.65 and total carbon dioxide of 50.1 volume per cent. Inhalations of carbon dioxide were given from three to ten minute periods several times per day. The Cheyne-Stokes type of respiration was absent for several hours after carbon dioxide treatment. Although dyspnea was augmented at start of carbon dioxide



treatment, it was markedly decreased for periods ranging from several to twenty-four hours after the inhalations. Cyanosis was absent on days on which carbon dioxide was given and her mental condition was improved. One-half per cent of hydrochloric acid solution with glucose and acacia was also given by the rectal drop method in from 300 to 500 cc amounts on two occasions.

After several days of this treatment the blood reaction had returned to normal,  $p_{\text{H}}$  7.411, total carbon dioxide 53.7 volumes per cent, with her physical condition markedly improved. On cessation of treatment for forty-eight hours or more the former symptoms returned together with a marked cyanosis and alkalosis,  $p_{\text{H}}$  7.649, total carbon dioxide 49.6 volumes per cent. Improvement of her physical condition was again brought about with a return of the blood reaction to normal using 10 per cent carbon dioxide and 90 per cent oxygen. Failure of cooperation on part of the patient made the treatments very difficult and later unwarranted. Her physical condition gradually became worse and death resulted from bronchopneumonia.

Postmortem findings by Dr. Bunting showed general arteriosclerosis, arteriosclerotic scars in kidney, cardiac dilatation, hypertrophy, chronic fibrous myocarditis, ventricular thrombi, pulmonary thrombosis and bronchopneumonia.

CASE 4—Male, aged 20, had acute arthritis, aortic and mitral insufficiency, myocarditis, chronic valvular disease. Patient was given potassium acetate, potassium citrate, 15 grains each, and sodium salicylate and sodium bicarbonate, 10 grains each, every three hours. Patient developed a very marked cyanosis and became extremely dyspneic and irrational. Respiratory rate mounted to from 50 to 60 per minute. Venous blood  $p_{\text{H}}$  7.563, total carbon dioxide 58.3 volumes per cent. Two days later he was still very cyanotic,  $p_{\text{H}}$  7.623, total carbon dioxide 57.1 volumes per cent. He perspired very markedly. Collected perspiration and reaction determined,  $p_{\text{H}}$  4.281. The alkali administration was stopped and from 500 to 1,000 cc of 0.5 per cent hydrochloric acid was given per day for three days. Cyanosis disappeared on second day, and on third day patient had a color indicating even higher oxygenation than normal,  $p_{\text{H}}$  7.451, total carbon dioxide 42.8 volume per cent. With disappearance of cyanosis patient again became rational. Dyspnea slowly disappeared and patient gradually recovered.

In the few cases that have come under our observation it seems as if there is a direct correlation between the production of cyanosis and certain types of alkalosis. In view of the theoretical possibility discussed above it is altogether probable that variations in the amounts of carbonic acid and sodium bicarbonate, both in ratio and absolute amounts, are responsible for a very definite physiologic distress due to the limiting of blood oxygenation.

It is suggested that a possible explanation of the above mechanism may be found in a disturbance of the normal shift of the chlorine ion between plasma and corpuscle. A study of the diagram of the circulation will permit a better discussion of this view. The rapid elimination of carbon dioxide from the blood thus causes a carbon dioxide deficit which, in turn, results in the passage of the sodium ion into the tissue fluids or partially in its excretion in the urine. The decreased sodium ion concentration thus prevents the transportation of the chlorine ion from the hemoglobin and so prevents the formation of oxyhemoglobin. The stimulation of the respiration from the anoxemia would result in the elimination of more carbon dioxide, thus really form-

ing a vicious cycle. The view that reduced hemoglobin ( $\text{HbCl}_2$ ) is more basic than oxyhemoglobin (L. Henderson<sup>3</sup>) might also enter as a factor, inasmuch as an excess of alkali in the plasma with low carbonic acid concentration may increase the basicity of the corpuscles, thus stabilizing the hemoglobin chloride combination<sup>4</sup>

#### CONCLUSIONS

The acid-base equilibrium is shifted toward the alkaline side during an acute clinical fever. If the fever is sufficiently high the alkalosis may result in distressing symptoms.

Fever alkalosis is very similar to that of voluntary hyperpnea or hot bath hyperpnea and is very probably due to the increased lung ventilation.

The acidotic tendency of starvation offsets, in part, the fever alkalosis. The actual change in  $p_{\text{H}}$  and sodium bicarbonate due to the fever is, therefore, greater than reported results.

A shift in the acid-base balance toward the alkaline side may apparently be of such a nature as to decrease the oxygenation of the blood. The concomitant occurrence of a cyanosis with a prolonged alkalosis and its disappearance upon counteracting the alkalosis has been observed clinically. Other factors operating concomitantly may, however, have been responsible for the changes<sup>28</sup>

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28 Since the writing of this paper a very interesting observation has been published by Morris (Anoxemia and the Increased Electrical Excitability of the Neuromyone, Brit J Exper Path 3 101, 1922) regarding the effect of alkalosis experimentally produced in cats and dogs on the oxygenation of the blood. His experiments show that an increase in the  $p_{\text{H}}$  value of the blood within certain limits produced by the injection of sodium carbonate (No  $\text{CO}_2$ ) decreases the oxygenation of the arterial blood and still more greatly decreases the amount of oxygen given up to the tissues. Evidence is also offered that the tetany of alkalosis is an effect of the resulting anoxemia. These observations are completely confirmatory of our clinical and experimental studies.

# PHYSICAL AND CHEMICAL STUDIES OF HUMAN BLOOD SERUM

## I A STUDY OF NORMAL SUBJECTS \*

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### INTRODUCTION

This work was originally undertaken in order to discover possible physical and chemical changes occurring in blood serum during those disturbances of water balance which result in the appearance or disappearance of edema. During the course of these studies, 172 sets of determinations have been made, and this paper presents the data from twenty-eight observations on eighteen normal subjects. The pathologic material will be discussed later. As we have failed to demonstrate any consistent changes accompanying such disturbances of water balance, this publication must be, in the main, a statistical report. We have been unable to find in the literature any previous studies of a similar nature that would demand a detailed discussion here. They are, in general, considerably less complete than this work or they present definite errors in method. The older work is well summarized in H. D. Hamburger's "Osmotischer Druck und Ionenlehre." Certain physical properties of the blood have been determined in this country by Gettler, Butterfield and others, but their studies have usually omitted a simultaneous determination of the chemical constituents.

### METHODS

The following determinations were made on each serum, freezing point depression, specific conductivity at 25 C, refractive index, chlorine,  $\text{HCO}_3^-$ , glucose, nonprotein nitrogen, total nitrogen, in certain cases urea and phosphorus, and more recently, sodium and potassium. All glassware was calibrated in the laboratory and the standard solutions were checked at frequent intervals. Duplicate determinations were made in practically every instance. When possible, all results are expressed in millimols per liter.

1 *Preparation of Serum*—Blood was drawn from an arm vein by means of a well oiled (liquid petrolatum) syringe and was delivered under from 2 to 3 cm of liquid petrolatum in 50 c.c. centrifuge tubes,

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\* From the Chemical Division, Medical Clinic the Johns Hopkins University and Hospital, and from the Department of Medicine of the College of Physicians and Surgeons of Columbia University and the Presbyterian Hospital.

thereby avoiding any exposure to air. In the collection of this blood a tourniquet was applied to the arm immediately before the vena puncture, but the period of stasis never exceeded two minutes. The blood was allowed to clot and, after separation of the clot with a glass rod, it was centrifuged. The serum was then removed at once and was almost invariably obtained without hemolysis. The time elapsing between collection of the blood and separation of the serum was about one hour. During the time involved in making the determinations, the hydrogen ion concentration of the serum did not change to exceed a range of from  $p_H$  7.7 to 7.4.

*2 Freezing Point Depression*—The standard Beckmann apparatus was used with a Heidenhain thermometer especially designed for cryoscopy. The usual precautions against overcooling were carefully observed and mechanical stirring was employed. The method was checked at frequent intervals by means of tenth molar potassium chlorid and 1 per cent sodium chlorid solutions. The freezing point of conductivity water determined the actual zero for each observation and controls were not accepted when differing by more than 0.005 C. In the process of obtaining such controls there were often several readings at great variance with the final result, and therefore, the somewhat uniform final results obtained in a series of bloods, tend to conceal these rather disturbing individual discrepancies. This fact leads us to doubt the value of cryoscopy as applied to blood serum.

*3 Electrical Conductivity*—The conductivity was determined by means of a Kohlrausch bridge designed by Leeds and Northrup. A constant speed motor generator producing a high frequency alternating current supplied the electromotive force. Calibrated Leeds and Northrup Curtis coils furnished the variable resistances. A series of oil condensers were used to balance the capacity of the cell. The conductivity cell was of the Ostwald type requiring about 4 cc of serum. The cell constant, which approximated 1.5, was determined by means of a standard tenth molar potassium chlorid solution before each observation. All determinations were made in a constant temperature water bath at 25 C and three different resistances were used in each determination. The results are expressed as specific conductivity  $\times 10^{-4}$ .

The effect of varying concentrations of protein upon the conductivity has been pointed out by Bugarszky and Tangl<sup>1</sup> and ourselves,<sup>2</sup> but it is impossible at present to give mathematical expression to this correction.

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1 Bugarszky, St., and Tangl, F. *Arch f d ges Physiol* **72** 531, 1898.

2 Palmer, W. W., Atchley, D. W., and Loeb, R. F. *J Gen Physiol* **3** 801, 1921, **4** 585, 1922.

# Normal

Date	Cause	Diagnosis	Freezing Point Expressed in °C	Specific Conductivity $\times 10^{-4}$	Multimols Cl	Multimols $\text{HCO}_3^-$	Multimols Na	Multimols K	Multimols Glucose	Multimols Urea	N per Serum	Protein per Cent	Refractive Index	Remarks
11/23/20	B	Normal	0.542	120.2	102.0	31.0	—	—	6.5	3.7	—	7.4	17.1	P = 0.6 millimols
11/23/20	L	Normal	0.541	118.7	103.3	31.0	—	—	6.1	6.2	29.3	7.6	17.0	P = 0.6, serum turbid
12/10/20	I	Normal	0.541	120.3	103.0	25.9	—	—	4.4	1.2	—	7.2	17.0	Serum turbid
2/15/21	B	Normal	0.541	121.1	101.7	32.1	—	—	—	—	21.3	7.5	17.2	Serum turbid
2/24/21	H	Normal	0.530	118.8	101.7	29.0	—	—	7.3	4.5	—	7.3	17.2	Serum turbid
3/1/21	F	Normal	0.529	121.0	105.1	30.1	—	—	5.1	6.7	33.7	7.3	17.4	Slight hemolysis
4/1/21	K	Normal	0.541	118.0	104.6	30.3	—	—	4.4	5.5	30.0	7.1	16.0	Serum turbid
4/1/21	K	Normal	0.539	121.6	105.3	28.2	—	—	4.2	7.0	30.9	6.9	16.1	Serum turbid
4/6/21	R	Normal	0.542	118.5	104.3	29.9	—	—	5.1	6.5	35.0	8.0	18.1	Serum turbid
4/26/21	Hb	Normal	0.541	119.8	101.7	31.5	—	—	3.7	5.2	30.0	7.4	17.1	Serum turbid
4/26/21	I	Normal	0.546	120.6	102.7	31.1	—	—	4.7	5.3	29.8	7.4	17.1	Serum slightly turbid
4/27/21	T	Normal	0.548	118.3	103.0	32.0	—	—	5.1	5.0	29.5	7.8	17.6	Serum slightly turbid
4/27/21	Ic	Normal	0.548	118.3	103.0	32.0	—	—	4.6	3.8	32.6	7.7	17.8	Serum slightly turbid
4/29/21	MeK	Normal	0.549	118.2	101.7	33.3	—	—	—	—	—	—	—	—
1/11/21	Lo	Normal	0.547	119.8	103.7	32.0	—	—	5.3	1.7	28.3	8.1	17.9	—
2/5/21	Lo	Normal	0.530	120.7	102.4	35.0	—	—	4.4	4.0	35.7	7.1	17.5	—
3/3/21	Lo	Normal	0.551	119.6	104.2	30.1	—	—	5.1	—	32.6	7.6	17.3	—
2/3/22	Lo	Normal	0.530 (?)	119.8	103.6	31.7	142.2	4.5	6.2	5.0	25.0	7.8	17.9	—
2/24/22	Lo	Normal	0.522	117.6	103.7	33.1	140.9	4.6	6.2	5.3	27.0	7.8	17.1	—
2/11/21	A	Normal	0.536	118.5	104.3	30.3	—	—	4.9	1.5	24.6	7.5	17.1	—
4/5/21	A	Normal	0.529	120.2	104.5	30.7	—	—	4.6	7.0	30.5	7.4	16.4	—
1/31/22	A	Normal	0.530	120.0	102.4	31.3	137.7	5.2	4.5	1.2	22.0	7.0	15.2	—
6/23/22	A	Normal	0.529	119.7	104.8	32.8	117.4	3.1	6.6	—	25.0	7.3	16.1	—
11/24/20	P	Normal	0.551	120.0	103.7	32.2	—	—	6.9	7.7	—	—	17.9	—
3/9/21	P	Normal	0.556	123.0	107.2	30.9	—	—	5.6	7.7	40.0	7.3	16.9	—
4/13/21	P	Normal	0.550	121.3	106.4	32.1	—	—	4.9	6.5	32.2	—	17.3	—
2/1/22	P	Normal	0.550	122.8	106.6	31.5	116.5	5.1	6.2	5.3	30.9	7.7	18.2	—
6/23/22	Be	Normal	—	116.5	101.4	32.8	111.2	4.5	6.2	—	25.0	8.0	17.8	—

\* Phosphorus in millimols

When serum, used in our experiments, was resaturated with carbon dioxide at alveolar tension, there was no significant change in electrical conductivity (less than 0.3 per cent). This would indicate that we were justified in ignoring the slight change in  $p_H$  due to loss of carbon dioxide.

The fact that the specific conductivity of a solution of sodium chloride is greater than that of an equimolecular solution of sodium bicarbonate explains the greater influence of the chlorine ion on the conductivity of serum. This fact may frequently be observed in our tables.

4 *Refractive Index*—An Abbé type of refractometer manufactured by Valentine and calibrated by the U. S. Bureau of Standards was used. The refractivity of conductivity water was determined each time, and from the differences between this figure and the index of the serum, the protein per cent of the serum was calculated according to Robertson.<sup>3</sup> The refractive index is expressed as  $n_D \times 10^{-3}$ . Temperature corrections are less than the limits of accuracy of the method and hence were omitted.

5 *Protein Per Cent*—(a) Calculated from refractive index as described above.

(b) The protein per cent was also determined in all cases as follows. Total nitrogen was determined in duplicate on 1 c.c. of serum by the Kjeldahl method and from this value was deducted the nonprotein nitrogen. This result, representing the protein nitrogen, was multiplied by 6.25 to determine the per cent of protein.

6 *Nonprotein Nitrogen*—This was determined by the method of Folin and Wu.<sup>4</sup>

7 *Urea*—This was determined by Marshall's method.<sup>5</sup>

8 *Glucose*—This was determined by the method of Folin and Wu.<sup>4, 6</sup>

9 *Carbonate Capacity*—This was determined by the method of Van Slyke<sup>7</sup> in calibrated pipettes.

10 *Sodium*—This was determined by the method of Kramer and Tisdall.<sup>8</sup> In our hands this method has not been entirely satisfactory in dealing with serum, although determinations on inorganic solutions were invariably correct.

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3 Robertson, T. B. *J. Biol. Chem.* **11**, 179, 1912.

4 Folin, O., and Wu, H. *J. Biol. Chem.* **38**, 81, 1919.

5 Marshall, E. K., Jr. *J. Biol. Chem.* **15**, 487, 1913.

6 Folin, O., and Wu, H. *J. Biol. Chem.* **41**, 367, 1920.

7 Van Slyke, D. D., and Cullen, G. E. *J. Biol. Chem.* **30**, 289, 1917.

8 Kramer, B., and Tisdall, F. F. *J. Biol. Chem.* **46**, 467, 1921.

11 *Potassium*—This was determined by the method of Kramer and Tisdall<sup>9</sup>

12 *Phosphorus*—This was determined by the method of Marriott and Haessler<sup>10</sup> This method was given up because the molecular concentration of phosphorus is too low to be of significance in this work

13 *Chlorids*—The chlorid method was devised by us and comprises parts of the Van Slyke and Donleavy<sup>11</sup> and the Wetmore<sup>12</sup> methods It is similar in principle to that described by Myers and Short<sup>13</sup> The technic of our method is as follows to 2 c c of serum are added 23 c c of distilled water and 15 c c of a saturated aqueous solution of picric acid The solution is filtered and to a 20 c c aliquot are added 5 c c of the standard silver solution described by Wetmore<sup>12</sup> The solution is agitated and allowed to stand for twenty minutes It is then titrated without filtration using the Wetmore thiocyanate solution The end-point is a definite change from light yellow to orange This method agrees accurately with the Van Slyke and Donleavy method and the distillation method of Bell and Doisy<sup>14</sup> All determinations were made in duplicate and titration variations of more than 0.06 c c were discarded

#### DISCUSSION

Little generalization and no detailed statistical analysis is justified by the limited amount of data presented It is interesting, however, to note that there are but relatively slight variations between determinations on the same and on different individuals, although the blood samples were collected without regard for time of day or diet

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9 Kramer B, and Tisdall, F F J Biol Chem **46** 339, 1921

10 Marriott, W McK, and Haessler, F H J Biol Chem **32** 241, 1917

11 Van Slyke, D D and Donleavy, J J J Biol Chem **37** 551, 1919

12 Wetmore, A S J Biol Chem **45** 113, 1920

13 Myers V C, and Short, J J J Biol Chem **44** 47, 1920

14 Doisy E A, and Bell, R D J Biol Chem **45** 427, 1920-1921

# PHYSICAL AND CHEMICAL STUDIES OF HUMAN BLOOD SERUM

## II A STUDY OF TWENTY-NINE CASES OF NEPHRITIS \*

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### INTRODUCTION

This paper presents fifty-two sets of observations on a series of twenty-nine cases of nephritis. The study includes five cases of acute nephritis, nine cases of uremia and fifteen cases of chronic nephritis, with and without edema. The scope of the investigation and the methods employed have been fully described in a previous communication<sup>1</sup>. We have found no new relationships between the laboratory findings and the clinical diagnosis, and therefore we shall omit detailed clinical descriptions.

### DISCUSSION

1 *Acute Nephritis*—These cases were typical but rather mild examples of acute nephritis with more or less hematuria. The serum analyses show no significant deviations from the normal figures except for an occasional increase in the nonprotein nitrogen. The serum chlorides were usually on the upper limit of normal. Attention may be called to the fact that the per cent of protein in the serum is seldom below the normal in spite of the presence of some edema.

2 *Chronic Nephritis*—A satisfactory classification of the conditions collectively known as chronic nephritis is impossible at the present time. It seems to us, however, that Widal's division of these cases emphasizing on the one hand nitrogen retention and on the other salt and water retention, affords today the most reasonable basis for clinical study. Among the seven cases of salt and water retention nephritis in our series, there are five which show a definite and unusual relationship hitherto undescribed. In all of our other cases, normal and pathological, there has been a rough but consistent relationship between the conductivity of the serum and its content of chlorin. For example, with a conductivity of 120, the chlorin content is usually about 103 millimols,

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1 Atchley, D W, Loeb, R F, Benedict E M, and Palmer, W W, Paper I of this series.



TABLE 1—ACUTE NEPHRITIS

Case	Diagnosis	Date	Freezing Point Depres- sion	Specific Conduc- tivity $\times 10^{-4}$	Milli- mols Cl	Milli- mols $\text{HCO}_3$	Milli- mols $\text{Na}$	Milli- mols $\text{K}$	Milli- mols Glucose	Milli- mols Urea	N P N Protein, per Cent			Refrac- tive Index	Remarks
											Mg per 100 C c Serum	Aldol	Refracto- meter		
I H H 45092	Acute nephritis	1/24/21	0.56	119.3	103.2	28.4	—	—	7.2	9.7	46.1	7.4	81	17.5	$\Gamma$ dema = $\pm$
		2/11/21	0.57	121.3	107.2	27.1	—	—	7.0	6.8	34.7	7.7	84	18.0	
I H H 45075	Acute nephritis	1/4/21	0.41	121.1	107.2	28.2	—	—	1.8	7.2	44.4	6.4	69	15.1	$\Gamma$ dema = +
		1/11/21	0.571	121.1	103.2	29.5	—	—	5.0	17.2	75.0	7.4	8.0	17.3	
		1/25/21	0.561	120.6	101.2	34.5	—	—	5.3	11.8	53.7	6.9	8.0	17.2	
		2/11/21	0.552	120.0	101.2	20.9	—	—	0.0	4.5	39.7	7.3	8.1	17.5	
I H H 45080	Acute nephritis	2/10/21	0.544	120.8	102.8	26.7	—	—	4.5	5	33.3	6.7	7.4	16.0	$\Gamma$ dema = $\pm$
		2/8/21		121.2	103.8	31.1	—	—	4.6	—	25.0	7.1	7.5	16.2	
P H 53653	Acute nephritis	1/13/22	0.524	122.8	108.6	25.4	146.4	5.1	7.0	3.7	19.0	6.6	7.1	15.5	$\Gamma$ dema = +
P H 53677	Acute nephritis	4/13/22	0.514	120.2	107.7	27.0	142.5	4.2	6.1	3.7	21.0	7.0	7.1	16.1	$\Gamma$ dema = +

TABLE 2—CHRONIC NEPHRITIS

Case	Diagnosis	Date	Freezing Point Depression $\times 10^{-4}$	Specific Conductivity $\times 10^{-4}$	Milib. mols Cl	Milib. mols HCO <sub>3</sub>	Milib. mols Na	Milib. mols K	Milib. mols Glucose	N P N Mg per 100 Gm Serum	Protein, per Cent	Refractive Index	Remarks
J H H 44662	Chronic nephritis with edema	10/29/20 11/4/20 11/10/20 11/15/20 11/21/20	0.544 0.533 0.548 0.536 0.549	129.6 127.7 127.9 128.2 130.4	103.6 107.3 106.0 105.3 106.3	30.5 32.9 31.7 32.1 32.3	— — — — —	— — — — —	6.6 5.7 4.8 5.6 4.8	— — — — —	4.4 4.8 4.2 4.1 4.1	5.6 5.9 5.6 5.4 5.4	Edema = +, P = 0.6 Edema = +, P = 0.5 Edema = +, P = 0.5 Edema = +, P = 0.8 Edema = +, P = 0.4 serum turbid
J H H 44662	Chronic nephritis with edema	11/30/20 12/2/20	0.554 0.563	131.0 133.3	110.3 114.7	32.2 30.0	— —	— —	5.0 5.1	— 43.5	4.2 4.2	5.5 5.7	Edema = +, P = 0.6 Edema = +, P = 0.4 after 10 gm of NaCl by mouth
J H H 44835	Chronic nephritis with edema	12/20/20 12/27/20	0.564 0.555	128.3 128.4	103.3 104.1	33.6 31.1	— —	— —	5.7 6.0	54.6 50.0	4.2 4.2	5.2 5.6	Edema = +, P = 0.6 Edema = +, P = 0.6
J H H 45256	Chronic nephritis with edema	1/29/21 2/25/21	0.522 0.533	118.6 123.6	103.8 105.1	— 29.9	— —	— —	1.3 1.9	— 20.5	4.2 4.3	6.7 6.5	Edema = +, P = 0.6 Edema = +, P = 0.6 serum turbid
J H H 45041	Chronic nephritis with edema	2/10/21	0.533	122.5	99.9	29.8	—	—	5.0	32.8	5.1	6.2	Edema = +
J H H 45226	Chronic nephritis with edema	1/5/21 4/9/21 4/11/21	0.550 0.555 0.549	130.7 125.1 124.4	107.9 107.9 106.9	28.3 28.6 28.7	— — —	— — —	4.7 1.6 —	36.6 44.4	5.4 5.6	6.2 6.1	Edema = +, P = 0.6 Edema = 0, serum slightly turbid
P H 18562	Chronic nephritis with edema	3/17/22	0.535	127.5	110.9	27.0	149.4	3.5	6.3	41.9	6.2	7.2	Edema = 0 Edema = +, P = 0.6 turbid
Ga H 44916	Hypertension, chronic nephritis	1/18/21 1/31/21	0.572 0.535	126.1 120.9	108.7 102.7	28.5 28.3	— —	— —	5.7 1.9	66.7 49.2	6.0 6.0	6.8 6.4	Edema = +, P = 0.6 Edema = +, P = 1.2 P = 1.0 P = 0.9 P = 1.2
Ro H 41591	Hypertension, chronic nephritis	11/2/20 11/5/20 11/9/20 11/12/20	0.507 0.532 0.580 0.569	124.0 125.6 122.2 122.1	109.3 110.8 104.7 104.8	24.8 24.4 27.6 29.8	— — — —	— — — —	1.2 8.1 6.7 5.6	18.0 20.7 17.2 14.5	7.4 7.3 — 7.3	7.9 7.5 8.0 8.0	Edema = +, P = 0.6 Edema = +, P = 1.2 P = 1.0 P = 0.9
J H H 44171	Hypertension, chronic nephritis	10/26/20	0.568	120.9	104.4	27.1	—	—	5.7	27.3	7.2	7.8	Edema = +, P = 1.2
Se H 15225	Chronic nephritis	3/7/21	0.553	120.1	102.1	27.8	—	—	5.2	21.3	70.5	6.4	Serum turbid
Bu H 46227	Chronic nephritis	3/21/21	0.552	118.9	101.1	28.5	—	—	7.1	7.2	37.0	7.2	Serum turbid
Ma H 45199	Chronic nephritis	2/11/21 3/1/21	0.526 0.540	119.9 121.0	100.1 102.8	32.7 27.2	— —	— —	4.2 4.7	22.5 24.3	6.2 6.9	7.1 8.1	Edema = +, P = 0.6 Edema = +, P = 1.2
Hl H 15189	Chronic nephritis	4/13/21 1/19/21 4/22/21	0.583 0.534 0.514	117.6 113.3 105.4	112.1 102.2 95.4	12.0 15.2 17.2	— — —	— — —	5.7 7.2 7.3	90.0 92.0 87.7	7.1 7.1 6.9	7.8 7.7 7.5	Edema = +, P = 0.6 Edema = +, P = 1.2 P = 1.0 P = 0.9
Tr H 15758	Chronic nephritis	1/22/21	0.536	119.7	106.6	19.1	—	—	4.7	16.8	61.2	7.3	Edema = +, P = 0.6
Ro H 18170	Chronic nephritis	3/15/22	0.508	111.6	102.7	27.8	196.5	1.9	5.8	—	27.9	7.9	Edema = +, P = 0.6

• Phosphorus in millimols

TABLE 3—URÆMIA

Case	Diagnosis	Date	Reducing Point Depos tion	Specific Conduc tivity $\times 10^{-4}$	Milli mols Cl	Milli mols $\text{HCO}_3$	Milli mols Na	Milli mols K	Milli mols Glu cose	Milli mols Ure	N P N Protein per Cent			Refrac tive Index	Remarks
											Mg per 100 Cc Serum	Kjel dahl	Refracto meter		
No., J H H 4326	Uremia	10/12/20	0.776	119.7	59.1	7.3	—	—	7.8	122.0	—	7.7	8.9	18.1	P* = 3.2
So., J H H 4009	Uremia	1/24/21 1/28/21	0.587 0.524	105.9 90.3	90.0 69.0	12.9 16.1	—	—	8.3 9.0	56.3 50.0	214.3 201.5	7.5 6.6	7.6 7.6	16.1 16.4	P = 2.3
Ku., P H 52266	Uremia	2/23/22	0.555	118.0	108.2	7.2	133.5	1.5	10.0	42.0	153.0	5.7	7.3	15.8	
Ke., P H 53317	Uremia	3/15/22	0.564	111.5	98.5	39.1	127.7	3.6	7.1	27.5	106.5	6.4	7.1	15.4	
Gr., P H 53551	Uremia	4/ 4/22	0.602	113.6	90.3	23.2	143.5	2.6	7.7	—	193.5	5.6	6.9	15.0	Idema = +
Co., P H 51009	Uremia	5/13/22	0.681	109.3	84.1	13.7	107.3	3.3	8.1	—	393.6	5.5	7.0	15.2	P = 6.1, edema = ++
W., P H 53725	Uremia	5/23/22	0.607	106.3	80.9	13.6	91.8	5.3	9.1	73.0	276.0	5.8	7.6	16.4	Edema = +
Noo., P H 54224	Uremia	6/ 2/22	0.676	122.5	108.0	6.3	129.2	5.0	9.3	65.1	—	5.9	8.2	17.6	Edema = +
Gut., P H 53761	Uremia	4/21/22	0.608	109.9	59.9	17.1	133.4	1.8	8.2	32.0	172.0	7.4	8.2	17.7	Idema = + + + + +, serum turbid

\* Phosphorus in millimols

and with a conductivity of 124, the chlorin concentration is about 109 millimols. In the five cases mentioned above the conductivity is distinctly higher than might be expected from the amount of chlorin present, whether the amount of chlorin be normal or increased, nor is this discrepancy explained by increased  $\text{HCO}'_3$  content. For example, patient Gr1 (Table 2) has a conductivity of 129.6 when the chlorin value was 105.6 millimols—a chlorin concentration within the limits of normal. In view of the work of Bugarszky and Tangl<sup>2</sup> and ourselves on the effect of protein concentration on electrical conductivity,<sup>3</sup> it was thought possible that the peculiar relationship between conductivity and chlorin concentration in these cases of nephritis might be the result of a smaller amount of protein in their sera. The case of R (Table 2) suggests, however, that this explanation may not be sufficient in itself. In this case there intervened between the first and second observations four days during which time the conductivity-chlorid discrepancy had disappeared without change in the chlorin or protein concentrations. It is interesting to observe that during this same interval the patient's edema disappeared.

In this work we have been unable to detect any consistent physical or chemical change occurring during the process of diuresis, and we were unable to find any undescribed changes in the cases of chronic nephritis with nitrogen retention.

3 *Uremia*—The low concentration of chlorin so frequently described in uremia was found in most of our cases. There was, however, no consistent diminution in the  $\text{Na}^+$  content coincident with this decrease in chlorin. The general dependance of the conductivity upon the chlorin concentration is well demonstrated in Table 3.

#### CONCLUSIONS

1 This paper presents the results of certain physical and chemical determinations on the sera of twenty-nine cases of nephritis.

2 A hitherto undescribed relationship between electrical conductivity and chlorin concentration ("conductivity-chlorid discrepancy") has been pointed out in certain cases of salt and water retention nephritis. In these cases the conductivity is definitely greater than would be expected from the chlorin concentration.

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2 Bugarsky, St., and Tangl, F. *Arch f d ges Physiol* **72** 531, 1898.

3 Palmer, W. W., Atchley, D. W., and Loeb, R. F. *J Gen Physiol* **3** 801, 1921, **4** 585, 1922.

# PHYSICAL AND CHEMICAL STUDIES OF HUMAN BLOOD SERUM

## III A STUDY OF MISCELLANEOUS DISEASE CONDITIONS<sup>3</sup>

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NEW YORK

### INTRODUCTION

In previous communications we have presented the results of certain physical and chemical observations on a series of normal individuals<sup>1</sup> and patients with renal disease<sup>2</sup>. In one of these papers,<sup>1</sup> we have described our methods in detail and have discussed the general purpose of the investigations. In this paper we have collected seventy-six sets of determinations on thirty-seven miscellaneous disease conditions. The group includes eleven cases of cardiac insufficiency with edema, six cases of diabetes mellitus, five cases of acute respiratory infection, two cases of toxæmia of pregnancy, three cases of cirrhosis hepatis with ascites, two cases of tuberculous pleurisy with effusion, two cases of diabetes insipidus, one case of cerebral hemorrhage, one case of pyloric stenosis, two cases of malignancy of the peritoneum, and one case of ascites of unknown etiology. As we have stated elsewhere,<sup>2</sup> case histories are omitted because no attempt is made to point out new relationships between clinical entities and the laboratory findings.

### DISCUSSION

1 *Cardiac Decompensation with Edema*—These cases are grouped together because they show more or less edema, primarily of cardiac origin. The underlying conditions responsible for the cardiac insufficiency include valvular disease, hypertension and chronic nephritis. From Table 1 it is quite apparent that we have observed no consistent physical or chemical changes in the serum accompanying the process of diuresis. For example, in case Sm, there is a considerable decrease in the freezing point depression, conductivity, and chlorine concentration with an increase in protein per cent, whereas, in Case Lo, there is a

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1 Atchley, D W, Loeb, R F, Benedict, E M, and Palmer, W W  
Paper I of this series

2 Atchley, D W, Loeb, R F, Benedict, E M and Palmer, W W  
Paper II of this series

TABLE 1—CARDIAC DECOMPENSATION WITH EDEMA

Case	Diagnosis	Date	Freezing Point Depression	Specific Gravity $\times 10^{-4}$	MmHg Cl	MmHg HCO <sub>3</sub>	MmHg Na	MmHg K	MmHg Glucose	MmHg Urea	N P N Protein, per Cent			Refractive Index	Remarks
											Mg per 100 C Serum	Kjehl dahl	Refractometer		
W1 I H H 44157	Hypertension cardiac insufficiency	10/27/20	0.332	121.0	103.2	29.4	—	—	6.2	13.0	—	7.1	7.5	16.2	Edema = 0, P = 1.9
		1/1/21	0.535	120.5	102.0	27.2	—	—	7.6	12.8	50.2	5.3	6.6	14.1	Edema = ++, bile tinged
P11 I H H 44669	Hypertension, cardiac insufficiency	1/4/21	0.540	124.2	103.1	31.8	—	—	6.3	8.1	46.2	5.5	6.0	13.4	Edema = +
		1/17/21	0.523	118.1	101.2	31.4	—	—	6.6	6.5	37.8	6.3	6.8	14.8	Edema = ±
P11 I H H 45139	Hypertension, cardiac insufficiency	10/27/20	0.539	119.8	107.8	26.1	—	—	6.0	15.5	—	7.1	7.1	16.0	Edema = ++, P = 0.8
		10/30/20	0.530	119.5	98.2	38.1	—	—	5.0	6.0	—	7.2	7.2	15.6	Edema = +, P = 0.5
B1 I H H 45714	Aortic insufficiency	11/6/20	0.511	117.5	102.3	33.3	—	—	5.7	—	—	7.9	8.5	18.2	Edema = 0, serum turbid, P = 0.7
		2/16/21	0.540	121.7	104.1	28.0	—	—	6.3	8.0	36.9(?)	6.1	6.9	15.1	Edema = +++
R1 I H H 45224	Cardiac insufficiency	2/18/21	0.541	121.0	98.3	35.6	—	—	1.3	6.0	37.7	6.2	7.1	15.1	Edema = ++
		3/8/21	0.538	119.9	101.4	32.0	—	—	5.7	—	29.5	6.9	7.6	16.5	Edema = 0
S11 I H H 45139	Hypertension, cardiac insufficiency	11/19/20	0.522	115.3	96.8	26.3	—	—	6.2	13.0	—	6.8	7.0	15.2	Edema = ++, P = 0.5
		2/21/21	0.548	123.5	107.2	25.8	—	—	5.8	7.2	36.6	6.9	7.6	16.1	Edema = ++
L1 I H H 45336	Hypertension, cardiac insufficiency	2/28/21	0.523	119.3	102.2	28.0	—	—	3.7	—	30.0	6.9	7.5	16.2	Edema = ±
		3/8/21	0.533	110.6	100.2	23.2	—	—	5.3	—	56.1	9.2	9.8	10.6	—
Ch I H H 45779	Cardiorenal disease	2/25/21	0.521	120.3	104.2	27.4	—	—	1.6	1.8	23.9	6.2	6.9	15.1	Edema = +
		3/4/21	0.570	121.5	106.1	27.9	—	—	1.6	10.7	18.0	6.6	7.0	15.2	Edema = ++
Pa P H 44216	Cardiorenal disease	3/7/21	0.536	120.1	102.2	26.9	—	—	7.7	7.5	31.1	6.3	6.7	11.6	Edema = ++
		1/28/21	0.514	120.9	107.3	27.6	—	—	1.5	6.8	32.9	6.9	7.1	15.1	Edema = ++, serum bile tinged
Lo P H 51287	Cardiorenal disease	3/7/22	0.517	125.1	113.6	23.6	137.1	1.7	7.5	13.6	55.0	6.8	6.6	11.5	Edema = ++
		3/8/22	0.512	125.5	114.8	24.7	142.2	1.7	7.6	13.7	12.0	6.1	7.0	15.2	Edema = ++ after theocoin
McT P H 52152	Cardiac insufficiency	3/27/22	0.519	125.3	115.3	16.9	139.8	4.7	5.1	19.0	71.0	6.0	7.1	15.5	Edema = ++
		6/5/22	0.521	111.5	95.7	25.1	105.2	3.1	7.5	—	61.0	6.1	6.8	11.9	Edema = ++
W1 P H 45811	Cardiac insufficiency	6/11/22	0.563	121.7	107.0	33.3	123.8	4.1	5.3	—	11.0	6.1	6.5	11.2	Edema = +
		5/7/22	0.533	120.6	107.6	28.1	149.0	4.5	5.6	—	23.0	7.3	8.0	17.2	Edema = +
W1 P H 45811	Cardiac insufficiency	5/23/22	0.519	119.6	100.7	31.8	118.7	5.2	7.1	4.8	23.4	7.2	7.7	16.7	Edema = ± after potassium ultrate by mouth
		5/25/22	0.466	110.5	95.7	27.0	—	3.7	6.1	—	20.0	7.2	7.2	15.7	Edema = ++

\* Phosphorus in millimols

TABLE 2—DIABETIS MELLITUS

Case	Disease	Date	Freezing Point Depression	Specific Gravity	Mmols Cl	Mmols HCO <sub>3</sub>	Mmols N <sub>2</sub>	Mmols Glucose	Mmols Urea	N P N M <sub>g</sub> per 100 C.e Serum	Protein, per Cent	Refractive Index	Remarks
I H 11653	Diabetes mellitus	11/13/20 11/29/20	0.515 0.512	116.3 116.1	98.5 102.2	29.9 29.5	— —	11.6 10.7	6.7 —	— —	6.1 6.8	7.8 8.1	P = 0.6, edema ± P = 0.4
I H 11654	Haemochromatosis, diabetes mellitus	10/11/20 11/1/20 11/29/20 12/15/20	0.609 0.604 0.604 0.600	111.2 119.1 117.8 109.3	100.2 97.3 97.9 91.9	21.3 31.5 29.9 22.9	— — — —	20.2 13.7 15.4 16.8	6.3 3.2 17.3 4.7	— — — —	— 7.1 6.2 7.2	11.1 7.2 7.2 9.7	P = 1.3, serum lipemic P = 0.6 P = 0.6 Serum lipemic
I H 11703	Diabetic coma	12/10/20	0.655	105.7	94.2	7.1	—	26.1	15.8	68.8	6.2	9.8	Serum lipemic
I H 11704	Diabetes mellitus	1/25/21 1/26/21	0.518 —	125.1 121.6	106.8 98.7	30.2 36.6	— —	10.6 10.9	3.7 2.7	30.0 33.1	5.4 5.9	6.0 6.6	Edema = +
H 63119	Diabetes mellitus	3/29/22	0.599	119.7	104.1	21.3	136.6	17.4	—	17.6	5.8	7.4	Edema = +, serum lipemic
P H 63550 and chronic nephritis	Diabetes mellitus	4/1/22	0.583	123.1	103.2	23.2	135.2	5.6	—	83.3	5.7	7.0	15.3

Phosphorus in millimols

TABLE 3—ACUTE RESPIRATORY INFECTIONS

Case	Diagnosis	Date	Freezing Point Depression	Specific Gravity	Mmols Cl	Mmols HCO <sub>3</sub>	Mmols Na	Mmols K	Mmols Glucose	Mmols Urea	Mg per 100 C.e Serum	N P N Protein, per Cent			Refractive Index	Remarks
												Kjehl	Refractometer	Protein		
A	Streptococcus sore throat	1/5/21 2/14/21	0.535 0.536	122.4 118.5	106.3 104.3	30.1 30.3	— —	— —	4.8 4.9	4.2 4.5	— 24.6	6.9 7.5	7.4 7.9	16.4 17.1		
Z	Pneumonia	11/14/20 11/16/20 12/1/20	0.525 0.511 0.541	113.8 113.7 120.3	95.6 96.1 101.5	28.4 29.4 32.7	— — —	— — —	6.2 5.6 —	8.8 7.3 7.8	42.5 — —	7.2 6.5 7.2	7.6 7.1 7.6	16.5 15.4 16.4		Second observation recovered P = 0.6 P = 0.6 P = 0.6
I H 11657	Pneumonia	1/20/21 1/25/21 1/28/21 1/31/21	0.483 0.522 0.544 0.551	107.9 110.9 112.7 114.3	88.4 88.2 94.0 95.8	29.5 33.0 30.1 29.8	— — — —	— — — —	5.9 8.2 8.6 9.4	5.2 46.1 12.2 12.2	28.6 46.1 57.2 43.4(?)	6.2 6.3 7.0 7.5	7.0 7.5 7.9 8.3	15.2 16.3 17.1 17.8		Serum bile tinged Serum bile tinged Serum bile tinged
I H 11701	Pneumonia	3/19/21 3/21/21	0.510 0.517	111.0 111.5	91.1 91.3	27.8 30.8	— —	— —	6.6 5.3	16.2 11.7	66.7 57.1	6.1 6.5	6.7 6.9	14.7 15.0		
M 5398	Pneumonia	5/10/22	0.495	111.8	92.5	28.4	115.1	3.5	8.3	—	31.3	6.0	6.9	15.0		

\* Phosphorus in millimols

TABLE 4—TOXEMIA OF PREGNANCY

Case	Diagnosis	Date	Freezing Point Depression $\times 10^{-4}$	Mull- mols Cl	Mull- mols $\text{HCO}_3$	Mull- mols Na	Mull- mols K	Mull- mols Glucose	N P N Mg per 100 C c Serum	Protein, per Cent Kjehl-Refractometer	Refractive Index	Remarks
I H H 10769 (Obs)	Eclampsia	10/21/20	0.551	107.3	13.3	—	—	13.5	—	6.4	7.9	17.1 P* = 0.8, serum Hbg tinged, patient had just been bled, edema = ++
		10/23/20	0.508	105.6	19.6	—	—	6.4	—	5.0	5.8	13.0 P = 0.8, edema = +
		11/ 8/20	0.531	104.8	27.8	—	—	6.4	—	7.4	8.3	17.8
Co I H H 10856 (Obs)	Eclampsia	12/ 2/20	0.510	102.2	21.3	—	—	3.9	21.0	6.0	6.9	15.0 P = 0.6, edema = ++, patient just bled
		12/ 6/20	0.523	95.7	38.1	—	—	5.3	20.8	5.4	6.1	13.6 P = 0.6, edema = +
		12/20/20	0.520	101.4	30.0	—	—	4.6	33.0	7.6	8.2	17.7
G I H H 10826 (Obs)	Eclampsia and endrhae insulinetenev	12/ 2/20	0.524	109.0	19.3	—	—	3.7	27.4	5.9	7.0	15.2 P = 0.6, edema = ++
		12/ 6/20	0.533	111.9	25.3	—	—	4.6	37.0	5.1	6.0	13.3 P = 0.8, edema = +
		12/ 7/20	0.542	112.9	24.0	—	—	4.9	30.0	5.3	6.1	13.5 P = 0.6, edema = +
		1/ 5/21	0.516	96.9	32.9	—	—	5.2	—	7.9	8.6	18.6
		1/17/21	0.521	100.3	31.5	—	—	5.2	31.9	7.8	9.0	19.1

\* Phosphorus in millimols

TABLE 5—CIRRHOSIS HEPATIS

Case	Diagnosis	Date	Freezing Point Depression $\times 10^{-4}$	Mull- mols Cl	Mull- mols $\text{HCO}_3$	Mull- mols Na	Mull- mols K	Mull- mols Glucose	N P N Mg per 100 C c Serum	Protein, per Cent Kjehl-Refractometer	Refractive Index	Remarks
P H 52949	Cirrhosis hepatis	3/12/22	0.498	100.0	27.5	124.7	4.2	7.2	26.0	6.8	7.3	15.8
Kc P H 50978	Cirrhosis hepatis	3/21/22	0.490	103.8	23.9	133.8	4.7	8.2	33.0	5.2	5.5	12.4
Co P H 36233	Cirrhosis hepatis	3/31/22	0.518	105.6	26.4	112.2	2.7	7.3	30.0	7.0	7.7	16.6 Na probably incorrect



TABLE 6—MISCELLANEOUS GROUP

Case	Diagnosis	Date	Fasting Blood Sugars	Specific Gravity	Mg mols Cl	Mg mols HCO <sub>3</sub>	Mg mols Na	Mg mols K	Mg mols Glu cos	Mg mols Urea	N Mg per 100 Grams	Protein, per Cent			Remarks
												Albumin	Reactive dihl meter	Reactive Index	
W H H 11729	Diabetes (cerebral hemor- rhage)	11/23/20	0.25	115.0	98.3	31.8	—	—	4.6	5.5	—	7.8	8.5	18.3	
W H H 11136	Psittac stenosis	9/21	0.21	96.9	60.5	45.9	—	—	7.9	—	88.2	8.1	8.9	10.0	
B H H 5691	Papillary cyst adenoma	1/15/22	0.529	118.2	103.2	31.1	140.0	1.3	6.3	—	16.0	7.6	7.9	17.1	
I H H 51729	Carcinoma of stomach	1/19/22	0.509	119.1	101.8	29.0	111.7	1.3	8.6	—	—	—	7.0	15.3	
S H H 15217	Diabetes insipidus	2/20/21 3/4/21	0.448 0.547	119.9 120.0	108.0 107.0	31.0 31.0	— —	— —	5.4 5.2	3.5 5.0	20.3 30.9	8.1 7.8	9.1 8.0	19.1 17.2	
H H H 51107	Diabetes insipidus	7/8/22 3/22/22	0.529 0.530	119.3 120.3	103.0 100.3	33.7 35.3	13.7 141.7	1.3 1.0	5.4 5.1	3.3 —	20.0 19.3	7.7 7.6	8.3 7.5	17.8 16.2	Pituitrin, 2 c.c. in prev vious 12 hours
H H H 53184	Tuberculous pleurisy	3/29/22	0.345	115.9	101.2	29.9	138.7	1.1	5.5	—	22.0	7.1	7.7	16.7	
I H H 53614	Tuberculous pleurisy	4/15/22	0.496	113.1	100.2	26.3	129.5	5.2	5.9	—	18.0	7.0	7.1	15.5	
M H H 16114	Achilles, cause undetermined	6/12/22	0.535	121.6	108.8	29.3	130.3	4.1	5.7	—	23.7	7.0	7.3	15.8	

marked increase in freezing point depression, conductivity, and chlorin concentration, with no change in the protein per cent. Although we have observed no consistent changes associated with diuresis, it is interesting to note that whenever there is a change in the amount of edema present, there is some coincident change in the physical or chemical properties. It has been impossible for us to predict the degree or direction of these changes. Quantitatively, however, they are very definite and usually exceed the maximal variations in a normal individual.

In the case of Pu, the changes during diuresis are quite unusual. This patient entered the hospital on two occasions separated by an interval of four months. On both admissions the patient had marked edema which disappeared rapidly following rest in bed and the administration of digitalis. The clinical improvement in both instances was accompanied by qualitatively similar changes in the blood serum. With a constant conductivity and protein per cent there was a considerable decrease in chlorin concentration with a simultaneous increase in the  $\text{HCO}'_3$  concentration. These variations in chlorin and  $\text{HCO}'_3$  concentrations do not appear to be equimolecular. Each time at the completion of diuresis, the serum returned to normal.

2 *Diabetes Mellitus*—The sera in these cases (Table 2) show no abnormalities that have not been frequently described.

3 *Acute Respiratory Infections*—In case A (Table 3), the blood was taken at the onset of an acute streptococcus sore throat and showed no deviation from normal other than a slight increase in conductivity and chlorin concentration. The other determinations were made on patients with lobar pneumonia and show the usual changes described in this condition.

4 *Toxaemia of Pregnancy*—Except for case Co (Table 4), no new facts are brought to light by the investigation of this group of cases. The case Co shows the same decrease in chlorin concentration and increase in a  $\text{HCO}'_3$  concentration with practically no change in conductivity and little change in protein per cent that was described above in case Pu of the cardiac series (Table 1). The changes in this instance, also, accompanied the loss of edema and, again the changes were not equimolecular.

5 *Cirrhosis Hepatis*—These three cases were classical examples of portal cirrhosis and it is interesting to note the wide spread variations in all of the determinations.

6 *Miscellaneous Group*—No conclusions can be drawn from the analysis of isolated cases and Table 6 is presented for statistical purposes only.

## BOOK REVIEW

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CLINICAL MEDICINE I Tuesday Clinics at the Johns Hopkins Hospital  
By LEWELLYS F. BARKER, M.D., LL.D., Visiting Physician to Johns Hopkins Hospital Cloth Price, \$7 net Pp 617, with 66 illustrations Philadelphia W. B. Saunders Company, 1922

The author states that this volume has been prepared to meet the request of many former students that a report of the work at his clinics be published. He furthermore, presents this work as a plea in defense of the amphitheater clinic or rather a modified type of such a clinic, in which the student participates.

A portion of the first chapter is devoted to the method of making a diagnosis. The author states that in an ordinary obscure case, in addition to the history, physical and ordinary laboratory examination, there should be included roentgenograms of dead teeth and paranasal sinuses, roentgenoscopic examination of the thorax and gastro-intestinal tract. Furthermore, the patient should be examined by the various specialists, and only after data from these various sources have been secured should the physician attempt to make a diagnosis. The question might arise as to how a student thus taught would make a diagnosis in case he engages in country practice or become a consultant.

He illustrates his method in the first clinic in a case in which the diagnosis of carcinoma of the bronchus is finally made. The author states that the history and physical examination pointed to the thorax as the seat of the trouble. The patient was given, however, a test breakfast, had roentgenograms made of teeth, sinuses, thorax, spine and the gastro-intestinal tract, and was examined by a laryngologist, a neurologist, a urologist and an orthopedist. It would appear that the diagnosis might have been arrived at much more directly and with less inconvenience and expense to the patient if a well trained internist had taken a careful history and made a physical and roentgen-ray examination of the chest. Cumbersome methods of making a diagnosis, with consequent added cost to the patient, should not be encouraged.

The author's free use of unfamiliar terms, such as "viremia," "tabagism," "cerebritis" and "abdominous" might confuse both student and practitioner. One sentence might be quoted to illustrate this point further. "The patient has therefore, not only an oliguria, albuminuria, cylindruria and hematuria, renal disease but also a hypochloruric, hypozoturic and hyposthenuric renal disease."

Thirty-one diseases are discussed in the clinic, including eight clinics on neurology. Dr. Barker's method of analysis of symptoms from the standpoint of pathologic physiology is highly commendable, as is also the method of teaching in which the students actively participate.

When, however, such clinics are put into book form much of the zest is eliminated. As the author states "No textbook and no manual can accomplish this so well as can a clinic conducted by a living human personality."

To the former student who can create a mental picture of the entire scene, no doubt this book will be read with both interest and profit. To others, however, seeking for specific information on some subject the search for such knowledge may prove quite wearisome. Perhaps its greatest value is for the teacher of medicine who provided he has not already adopted this dialogue method of imparting knowledge can profitably peruse the pages of this book.

## OBSERVATIONS ON THE VALUE OF PHENOLTETRA- CHLORPHTHALEIN IN ESTIMATING LIVER FUNCTION \*

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In 1913, Rowntree, Hurwitz and Bloomfield,<sup>1</sup> in making a résumé of all known methods for testing the functional capacity of the liver concluded that they were all of little value in that they did not deal with functions specific to the liver. They made the possible exception of the urobilinogen test, which they found positive in most mild diseases of the liver, but it gave no information as to the extent of liver injury, as it entirely lacked the quantitative side. It was of no value, therefore, from the standpoint of prognosis.

During the course of a pharmacologic search for a cathartic of protracted action, it was discovered by Rowntree and Abel<sup>2</sup> in 1909, that phenoltetrachlorphthalein was eliminated entirely by the liver, and they described its properties. They found it to be an odorless, tasteless chrystalline substance, insoluble in water and forming deeply colored hydrolizable salts with alkalies. They found its avidity as an acid not far removed from phenolphthalein. Its ionization constant has not been determined. The dye was first prepared by Orndorff and Black<sup>3</sup> in 1908.

Rowntree and his associates first advocated the use of tetrachlorphthalein to test the functional capacity of the liver. They injected 8 c c (400 mg) of the dye diluted to 100 c c with physiologic solution of sodium chlorid intravenously by the gravity method. Catharsis was instituted at 6 a m with Epsom salts and the dye injected at noon,

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\* From the Gastro-enterological Clinic of the Graduate School of Medicine of the University of Pennsylvania.

\* Read before the Association of American Physicians, Washington, D C, May 4, 1922.

1 Rowntree, Hurwitz and Bloomfield. Experimental and Clinical Study of the Value of Phenoltetrachlorphthalein as a Test for Liver Function, Bull Johns Hopkins Hosp 23 327, 1913.

2 Abel, J J, and Rowntree, L G. On the Pharmacological Action of Some Phthaleins and Their Derivatives, with Especial Reference to Their Action as Purgatives. J Pharmacol & Exper Therap 1 231, 1909.

3 Orndorff, W R, and Black, J A. Phenoltetrachlorphthalein and Some of Its Derivatives, Am Chem J 41 349, 1909.

followed by cathartic pills, if necessary. Little attention was paid to the diet. Stools were collected for forty-eight hours following the injection. The dye was separated from the stool, and the amount excreted was estimated in the Rowntree-Geraghty modification of the Autenreith Koenigsberger colorimeter. They experimented on dogs with biliary fistulas and found that the dye appeared free in the bile in fifteen minutes following its intravenous administration, and that in forty-eight hours, from 35 to 55 per cent of it could be recovered in the feces. Their studies indicated that the excretion of tetrachlor would be useful in the estimation of the functional capacity of the liver.

Whipple, Pughtal and Clark<sup>4</sup> showed that the normal output of dye in the feces of dogs was remarkably constant, and that the drop in tetrachlor output ran parallel to the amount of liver injury. Passive congestion of the liver of moderate degree caused little impairment of function and showed a normal output of dye. They found that destruction of liver tissue by the actual cautery caused a prompt drop in the tetrachlor output. Delay of dye excretion from such an injury was present but could not be demonstrated in work with the feces. They found the urine of dogs free from dye or, at most, only a trace (pink on adding alkali), following the injections.

Sisson<sup>5</sup> found the normal output of dye in the feces to be about 35 per cent. He reached no definite conclusion as to the clinical value of the test.

Chesney, Marshall and Rowntree<sup>6</sup> found the lower limit of dye elimination in the feces to be 30 per cent of the amount injected in forty-eight hours. The dye was never found in the urine in health after the administration of 400 mg, according to these observers.

Krumbhaar,<sup>7</sup> in 1914, in summarizing the status of functional liver tests, concludes that although no satisfactory single test for the functional capacity of the liver has yet been accepted, the tetrachlor test of Rowntree promises the greatest value. McLester and Frazier,<sup>8</sup> in 1915, following Rowntree's technic, concluded that "this test taken alone in its present form is of no value clinically." Kahn and Johnston,<sup>9</sup> in

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4 Whipple, Pughtal and Clark. Tests for Hepatic Function and Disease Under Experimental Conditions, *Bull Johns Hopkins Hosp* **24** 343, 1913.

5 Sisson, W. R. A Clinical Study of Two Hepatic Functional Tests, *Arch Int Med* **14** 804 (Dec) 1914.

6 Chesney, A. M., Marshall, E. K., and Rowntree, L. G. Studies in Liver Function, *J A M A* **63** 1533 (Oct 31) 1914.

7 Krumbhaar, E. B. Present Status of Functional Liver Tests, *New York M J* **100** 719 (Oct 10) 1914.

8 McLester, J. S., and Frazier, B. Phenoltetrachlorophthalein Test for Liver Function, *J A M A* **65** 385 (July 31) 1915.

9 Kahn, M., and Johnston, J. B. The Phenoltetrachlorophthalein Test for Liver Function. *New York M J* **102** 848, 1915.

1915, following the same technic, reached a similar conclusion after studying a series of thirty-four cases

In 1916, McNeil<sup>10</sup> modified the Rowntree method by inserting the duodenal tube into the duodenum and injecting 400 mg of the dye. He recorded the time of first appearance of the dye in the bile. The bile was obtained by aspiration. He collected all the bile excreted in two hours in this way and estimated the percentage recovered. The difficult and cumbersome technic of the feces method and the conflicting opinions regarding its value, stimulated him in the study. He found that the dye first appeared in the bile normally (six cases) in from twelve to twenty-one minutes and that the total amount recovered through the duodenal tube in two hours varied from a trace to 10 per cent. The greater part of the dye was excreted during the first hour. The first appearance time of the dye in five cases of Laennec's cirrhosis varied from twenty-eight to forty-five minutes. He found a normal output of dye in three of these cases and practically no dye was recovered in two cases. He concluded that the dye elimination was of little value, but that its appearance time was decidedly delayed in certain pathologic conditions of the liver. Kahn,<sup>11</sup> in 1921, modified this procedure somewhat by stimulating the flow of bile into the duodenum. He administered a solution of magnesium sulphate and aspirated every ten minutes.

Aaron, Beck and Schneider<sup>12</sup> modified the duodenal technic and introduced a stable preparation of the dye. They believe that the quantitative estimation of the dye excreted is of little value, owing to the uncertainty of the quantity passed out through the bowel. Consequently, they were satisfied with estimating the time of appearance of the maximum color. They made it possible to get a much more reliable appearance time of the dye by establishing a drip from the tube. This was accomplished by the administration of 500 c c of water by mouth and injection of the dye after a steady drip from the tube was established. They reported 17.2 minutes as the average appearance time of the maximum color in the bile in sixteen normal cases, whereas the average in six pathologic cases was thirty-two minutes.

Summarizing the work which has been done, we conclude that the study of Rowntree, Hurwitz and Bloomfield, and of Whipple, Pughal

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10 McNeil, H. L. The Quantitative Estimation of Phenoltetrachlorophthalein Excreted in the Fresh Bile in Disease of the Liver, *J. Lab. & Clin. Med.* **1**: 822, 1915.

11 Kahn, M. Phenoltetrachlorophthalein Test on the Duodenal Content, *J. A. M. A.* **77**: 41 (July 6) 1921.

12 Aaron, A. H., Beck, E. C., and Schneider, H. C. The Phenoltetrachlorophthalein Test for Liver Function, *J. A. M. A.* **77**: 1631 (Nov. 19) 1921.

and Clark carried out both clinically and experimentally have proved the following

- 1 That since phenoltetrachlorophthalein is eliminated solely by the bile in health, it makes an ideal substance for testing the function of the liver

- 2 That the forty-eight hour output of dye in the feces is fairly constant in health

- 3 That the time of appearance of the dye in the bile is of decided importance, but it cannot be determined by the feces method

- 4 That the dye output decreases as the hepatic parenchymal damage becomes more extensive Chesney et al and Krumbhaar confirmed their clinical findings, whereas Sisson, McLester and Frazier, and Kahn and Johnston concluded that the test was of no clinical value

In view of the difficulty of carrying out the test and the lack of sufficient clinical confirmation it has not been widely adopted The more recent work of McNeil, Aaron et al with the duodenal tube has, we believe, opened up a new field for investigation We were stimulated to go on with this work and attempt to arrive at some definite conclusion, feeling that in view of the demonstrated merit of tetrachlor, a technic could be developed which would make this test in some measure comparable to the phenolsulphonephthalein kidney test After following Aaron's technic in a few cases, it was decided to enlarge on it in order to gather a maximum amount of information The series presented includes fifty cases, normal and pathologic The data recorded include the appearance time of the first faint pink, the appearance time of the maximum color and the number of milligrams of dye eliminated by the liver and obtained from the duodenum during a period of two hours when collected at half hourly intervals

It is interesting to note that in a number of normal cases, after the test was completed, the urine failed to show the presence of any of the dye

#### OUTLINE OF PROCEDURE

- 1 The duodenal tube (any type of tube) is passed into the stomach, so that the tip is at a point approximately twenty-one inches from the lips It is introduced in the morning on a fasting stomach for two reasons (a) the tube passes through the pylorus more quickly on the morning fasting stomach, (b) the liver is always in the same physiologic condition at this time, its digestive function not being exercised

- 2 The stomach is washed by giving two glasses of water by mouth and aspirating until clean Sixty c c of water is introduced into the stomach to be retained

3 The patient is turned on the right side and the tube is very slowly pushed downward by the patient until the tip is at a point twenty-seven inches from the lips. Lyon's method was used, allowing twenty minutes for the introduction of the tube to this point, the patient being instructed to breathe deeply and swallow slowly. If the tube does not pass the pylorus, it is pulled out to the twenty-one inch mark and the procedure is repeated. The passage of the tube into the duodenum rarely takes longer than one hour, barring organic obstruction, adhesions, persistent pylorospasm, or severe degrees of atony or ptosis. To ascertain whether or not the tip of the tube is in the duodenum does not present difficulty. The following points indicate its presence in the duodenum: (a) Presence of the duodenal tug, i. e., if the tube is in the duodenum, the plunger of the aspirating syringe will return to its previous position when traction is made on it. It pulls out easily, as a rule, when the tube is in the stomach. The water left in the stomach can usually be aspirated if this is the case. An exception occurs to this rule, if the tube is kinked in the stomach. (b) Appearance of pure yellow alkaline bile on aspiration. (c) Appearance of golden yellow froth. (d) Failure to obtain water in the syringe on aspirating after half a glass has been taken by mouth. (e) Lyon's stethoscope method. (f) Thirty c c of warm water allowed to run into the duodenum by gravity, the tube lowered and water syphoned back. If the tube is in the duodenum, the water will return bile stained. This procedure opens the sphincter of Oddi and causes bile to be expelled. This is probably the most reliable method when all others fail. It has not been necessary to resort to the fluoroscope. If the procedures are carried out in the order as given above, a definite decision as to the location of the tip can usually be made.

4 Just as soon as the tube enters the duodenum, 500 c c of water is given by mouth. The dye is not injected until a steady drip of bile stained fluid is coming from the tube. This step, introduced by Aaron and his co-workers, is an important one.

5 One hundred and fifty mg of the disodium salt of phenoltetrachlorophthalein as prepared in ampouls by Hynson, Westcott and Dunning (each c c containing 50 mg) is injected into a vein and the time of injection is recorded.

6 The bile is allowed to drip out into a white basin containing 3 or 4 c c of a 40 per cent solution of sodium hydroxid.

7 The time of appearance of the first faint pink color is recorded. The syringe is not to be used. If it is necessary to aspirate, the appearance time cannot be considered reliable. Aspirating every ten minutes, as advocated by Kahn, would render the appearance time of little value,



as a delay of more than nine minutes might thus escape recognition Kahn suggested the use of magnesium sulphate to stimulate the flow of bile, this is unnecessary when the water is given by mouth As Einhorn has shown, a solution of magnesium sulphate when introduced into the duodenum stimulates the liver, but the question at issue now is how the liver functions under normal conditions and not when under the influence of a stimulant

8 The appearance time of the maximum color, which is a deep purple, is recorded

9 Each half hour's output is allowed to drip into a separate basin Each basin must contain not more than 5 c c of a 40 per cent sodium hydroxid solution It is important to avoid using an excess of alkali as it makes the bile pigments more difficult to precipitate In addition it gives the solution a reddish tint which cannot be compared with the standard dye The time of injection was taken as the starting point of the two hour period, and not time of first appearance of the dye

10 A continuous slow drip from the tube should be maintained throughout the two hour interval This can be accomplished by having the patient drink a glass of water every half hour

To estimate the amount of dye eliminated, the procedure is as follows In the absence of a suitable colorimeter, we made up standard solutions containing a known amount of dye dissolved in 1,000 c c of water, 100 c c of each of these known solutions of the dye was placed in a thoroughly washed 100 c c bottle and tightly stoppered The bottles used as standards represent the following amounts of dye in mg 0.1, 0.2, 0.3, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12.5, 15, 17.5 and 20, respectively These solutions will remain practically unchanged for from four to six weeks, when a slight precipitate forms, due to the alkali of the disodium salt uniting with the silicate of the glass bottle

Each half hour's output is run through as follows (a) Pour the sample of dye laden bile into a 1,000 c c stoppered graduate Add sufficient 40 per cent sodium hydroxid solution to bring out the maximum intensity of color Avoid an excess because it makes it more difficult to precipitate out the bile pigments If this occurs a few drops of nitric acid should be added and the fluid realkalized with hydroxide until the color appears again Dilute to 1,000 c c and shake (b) Measure out 100 c c of this solution in a graduate and add about 3 c c of a saturated solution of basic lead acetate and 2 c c of a saturated solution of calcium chlorid The acetate solution precipitates the bile pigment and the calcium chlorid seems to assist particularly in those specimens which contain a considerable quantity of bile (c) Pour into a 100 c c test tube and heat in a water bath until the pre-

precipitate is being agitated. This requires but a few minutes. (d) Filter to remove the precipitate. (e) Pour into a bottle similar to those containing the standard and make comparative readings.

Dr Edgar N Cowan of the department of Biochemistry of the Graduate School of Medicine of the University of Pennsylvania, kindly worked out this method of precipitating the bile coloring matter.

Of the fifty subjects studied, thirty-five suffered from a great variety of clinical conditions. Fifteen had normal livers. In order better to appreciate the significance of the results, they have been tabulated into four groups (Tables 1, 2, 3 and 4).

*Table 1*—As far as can be ascertained clinically, these subjects have normal livers. Three of them were tested before the technic for the

TABLE 1—OUTPUT, 19 MG OR MORE, FIFTEEN CASES

Name	Age	Diagnosis	First Ap- pear- ance Time of Dye, Min	Time of Maxi- mum Inten- sity of Color, Min	Out- put in Mg First Half Hour	Out- put in Mg Second Half Hour	Out- put in Mg Third Half Hour	Out- put in Mg Fourth Half Hour	Total Out- put in Mg	Time of Total Out- put, Hours
Pic	21	Normal	10	11	10.0	6.2	7.5	1.5	25.2	2
Bis	51	Normal	8	11	4.0	10.0	2.0	8.0	24.0	2
Bar	38	Normal	11	13	4.0	6.0	6.0	3.0	19.0	2
Dro	30	Normal	8	11	8.0	12.0	1.5	0.0	21.5	2
Roa	22	Normal	11	14	6.5	5.0			11.5	1
Grc	37	Normal	9.5	15						
Kran	55	Normal	8	9.2						
Amb	40	Chr cholecystitis	9	14						
Darl	52	Chr cholecystitis	7	9	3.7	4.5	15.0	0.15	23.35	2
Kraf	65	Chr cholecystitis	10.5	15	9.0	3.0			12.0	1
Mel	34	Chr cholecystitis	7.5	10.5	9.0	5.0	2.0	3.0	19.0	2
Aur	17	Chr appendicitis	7	8.75	6.0	10.0	6.0	5.0	27.0	2
Go	27	Psychoneurosis	10	13	1.5	1.0	15.0	2.5	20.0	2
S. B.	30	Gastric neurosis	7	11	2.0	12.5	2.0	4.0	20.5	2
A. S.	36	Pernicious anemia	5	9	9.0	10.0	2.5	3.0	24.5	2
		R. B. C., 4,000,000								
Average	36		8.56	11.56	6.05	7.1	5.95	3.01	22.4	2

quantitative estimation was perfected. They were placed in this group because their livers were clinically negative and their dye appearance time more closely conformed to the average time appearance for this group. In two of the cases the output for the first hour only was taken. Their first hour output corresponds to the average first hour elimination for this group. Seven of the fifteen cases had no disease or their diagnosis was undetermined. None of them had fever or any indication of toxemia. In four cases a diagnosis of chronic cholecystitis had been made. There was one case each of chronic appendicitis, psychoneurosis, gastric neurosis and pernicious anemia. The patient with pernicious anemia was in good condition. His red cell count was 4,000,000 as he had had a transfusion recently. The ages of this group ranged from 17 to 60 years. The youngest, a girl of 17, had the highest

output of dye (27 mg) A young man of 21 was next with an output of 25.2 mg The average elimination for two hours was 22.5 mg, the output ranging from 19 to 27 mg The average elimination for the first hour was 13.1 mg, and for the second hour 8.9 mg The greatest output of dye occurred during the first hour in health The first appear-

TABLE 2—OUTPUT, FROM 10 TO 19 MG, SEVENTEEN CASES

Name	Age	Diagnosis	First Ap- pearance Time of Dye, Min	Time of Maxi- mum Inten- sity of Color, Min	Out- put in Mg First Half Hour	Out- put in Mg Second Half Hour	Out- put in Mg Third Half Hour	Out- put in Mg Fourth Half Hour	Total Out- put in Mg	Time of Total Out- put, Hours
Shee	50	Hypertrophic cir- rhosis, liver 4 fin- gers below costal margin chronic cholecystitis	9.5	19.5	1.5	3.0	5.0	0.5	10.0	2
For	73	Congestion of liver, edge 2 fin- gers below cos- tal margin myo- carditis	11	16	3.0	8.0	1.0	0.5	12.5	2
Wag	50	Severe diabetes, liver to umbilicus	14	14	2.0	5.0	2.0	1.5	10.5	2
Res	73	Diabetes, gan- grene chronic nephritis	8.5	11.5	8.0	2.0	1.0	0.5	11.5	2
Con	40	Diabetes	12	16	0.5	4.5	1.0	5.0	11.0	2
Wal	62	Arteriosclerosis	13	17						
Pei	64	Moderate arterio- sclerosis	12.5	13.5						
Ira	30	Cholecystitis, chr appendicitis pul- monary tubercu- losis	14							
Ercl	66	Chr cholecystitis cholelithiasis, periduodenal ad- hesions	25	26	4.0	7.0	0.75	0.1	11.85	2
Gre	50	Chr cholecystitis	8.5	14	6.0	5.0	2.0	3.0	16.0	2
Koe	52	Carcinoma of stomach, severe secondary ane- mia, liver neg	7	10	6.0	1.5	2.5	4.0	14.0	2
Brin	47	Osteoarthritis	8	12	5.0	3.0	2.5	3.0	13.5	2
F O H	53	Acute multiple arthritis	9	10	2.0	2.0	6.0	1.0	11.0	2
S L	26	Convalescent pneumonia	12	16	2.5	2.0	0.75	9.0	14.25	2
Mor	36	Chronic catarrhal sigmoiditis	8	10	6.5	3.0	1.0	0.5	11.0	2
Rieh	38	Chronic ulcerative colitis	10	16	10.0	0.25	0.25	0.0	10.5	2
Mak	51	Multiple sclerosis (5 years)	9.0	15	4.5	4.0	1.5	1.5	11.5	2
Average	48		11.2	14.8	4.39	3.58	1.9	2.15	12.79	2

ance time varied from five to eleven minutes with an average of 8.6 minutes The appearance time of the maximum intensity of the dye varied from 8.75 to 15 minutes, with an average of 11.6 minutes The first appearance time in McNeil's series of five normal cases was from twelve to twenty-one minutes We believe his later appearance time may be explained by two factors (1) use of the gravity method

of administering the dye, and (2) unreliability of the aspiration method. In certain cases when the sphincter of Oddi is not open, the aspiration method may give erroneous results as pointed out above in discussing the technic. McNeil emphasizes the fact that the entrance of bile into the duodenum is controlled by contraction of the gallbladder, and that some cases of supposedly delayed excretion time might be due to failure of the gallbladder to contract. The contraction of the gallbladder is not necessary in order to obtain the flow of bile into the duodenum. Almost any solution poured into the duodenum will cause an opening of the sphincter and a pouring out of bile even in the absence of a gallbladder. It is not necessary to obtain gallbladder bile in this test, although we believe that a variable amount is usually expelled. The administration of water by mouth, thus insuring a steady drip from the tube, is enough to keep the bile flowing.

Aaron et al. report 172 minutes as the average maximum color appearance in sixteen normal cases, using 75 mg of dye, as compared to our average of 116 minutes with 150 mg of dye. We feel that this latter amount of dye should be used when a quantitative estimation is to be carried out, as it is easier to work with larger amounts of dye in making comparisons with the standards.

*Table 2*—This includes seventeen cases in which the elimination is from 10 to 19 mg. Three of these cases have only the appearance time recorded. They were classified here because the time of appearance of the dye was similar to the average for this group. Three patients had definitely enlarged livers. Their dye output was very nearly identical, averaging 11 mg (50 per cent of the normal). The output of dye in three diabetics averaged only 11 mg, there being but 1 mg difference between the extreme figures (10.5, 11.5 mg). Seven cases can be classified as chronic infectious processes, in any one of which the liver might easily become involved secondarily. This subgroup includes one case each of infectious arthritis, osteo-arthritis, chronic catarrhal sigmoiditis, and chronic ulcerative colitis, and one case of chronic cholelithiasis with obstruction and periduodenal adhesions. However, there was nothing which clinically suggested hepatic insufficiency. It is in this type of case in which the liver is clinically negative, that the test should be of particular value. There is one case each of multiple sclerosis, convalescent pneumonia and carcinoma of the stomach in this group. The average first appearance time is 112 minutes as compared to 86 minutes of the normal group. The average maximum color time is 148 minutes as compared with 116 minutes of the normal group. The average dye output is 12.79 mg, that for the normal group is 22.9 mg.

Table 3—This includes eight cases in which the elimination is from 5 to 10 mg. Three cases of advanced cardiovascular disease in which a diagnosis of liver disease had not been made show a distinctly lessened dye output and a slightly delayed appearance time. A definite diagnosis of cirrhosis of the liver had been made on another. Still another presented active manifestations of tertiary syphilis but no evidence of liver disturbance. One patient was convalescing from a

TABLE 3—OUTPUT, FROM 5 TO 10 MG., EIGHT CASES

Name	Age	Diagnosis	First Ap- pearance Time of Dye, Min	Time of Maxi- mum Inten- sity of Color, Min	Out- put in Mg First Half Hour	Out- put in Mg Second Half Hour	Out- put in Mg Third Half Hour	Out- put in Mg Fourth Half Hour	Total Out- put in Mg	Time of Total Out- put, Hours
H/b	63	General arterio- sclerosis, cardiac hypertrophy, chr endocarditis, coronary sclero- sis, syphilis	11	16	2.5	2.5	0.75	1.5	7.25	2
Jack	45	General arterio- sclerosis, aortic regurgitation	8	15	2.0	1.0			3.0	1
Mars	68	Aortitis, Cor- bovinum, enlarg- ed mediastinal lymph nodes cholelithiasis (no obstruction), acute attacks, no HCl	10	13	2.0	2.0	1.0	1.0	6.0	2
Con	32	Cirrhosis of liver, syphilis	12	18	3.2	0.1	2.0	2.5	7.6	2
W H	36	Tertiary syphilis, Wassermann ++++	10	14	2.0	1.0	1.5	0.6	5.1	2
Arm	31	Convalescent pneumonia, ery- sipelas, nonhe- molytic strepto- coccus bacter- emia	7	14.5	0.1	2.0	1.75	3.0	6.85	2
Elsa	40	Convalescent, op- eration for chr appendicitis, chr pelvic disease, gastric neurosis, vagotonia	11	11	7.0	2.0	0.75	0.0	9.75	2
Yan	15	Colonic stasis	11	24.5	2.5	2.0	0.2	1.5	6.2	2
Average	40		9.87	15.75	2.66	1.57	1.13	1.44	6.96	2

severe streptococcus pneumonia, which may account for his low dye output. The other two patients were suffering from chronic infectious conditions of the abdomen. Whether these infections were severe enough to cause liver disturbance we could not determine. The average first appearance time was 9.87 minutes as compared to 8.6 of the normal group. The average maximum color time was 15.75 minutes as compared with 11.6 minutes in the normal group. The average dye output was 6.96 mg., that for the normal group was 22.4 mg.

*Table 4*—This table includes ten cases in which the elimination is under 5 mg. In this group we have placed patients whose clinical diagnoses include liver incompetency and whose dye output was less than 5 mg (under 25 per cent of normal). Three of them had far advanced cardiovascular disease, one had portal cirrhosis and another had a moderately congested liver. In three of them the delayed appear-

TABLE 4—OUTPUT, LESS THAN 5 MG., TEN CASES

Name	Age	Diagnosis	First Ap- pearance Time of Dye, Min	Time of Maxi- mum Inten- sity of Color, Min	Out- put in Mg First Half Hour	Out- put in Mg Second Half Hour	Out- put in Mg Third Half Hour	Out- put in Mg Fourth Half Hour	Total Out- put in Mg	Time of Total Out- put, Hours
Pem	60	Convalescent acute nephritis, myocarditis, cholecystitis, bile and urine cultures, staphylococcus aureus and albus	21.5	29.5	1.0	2.0	0.3	0.0	3.3	2
Dro	49	Arteriosclerosis, aortic aneurysm, mitral stenosis	13	17	0.5	0.4	0.2	0.1	1.5	2
Har	53	Arteriosclerosis, cardiac hypertrophy, chronic nephritis	14	34	0.1	1.5	0.3	0.0	1.9	2
Adley	64	Portal cirrhosis, aortitis	16	26	1.0	1.5	0.3	0.0	2.8	2
Hol	37	Distorted duodenum from periduodenal adhesions, cholecystitis, proved by operation	10	19	0.1	1.0	3.0	0.0	4.1	
E. B.	50	Cholecystitis (stones), hepatitis, moderate congestion	11.5	25						
Boa	39	Cholelithiasis (partial obstruction), operated, bladder full of stones, 10 in common duct	13	21.5	1.5	1.5	0.0	0.0	3.0	2
Rob	33	Partial common duct obstruction	15	None						
W. Sal	62	Cholelithiasis, obstruction common duct, small amount of bile	11	23	0.5	0.4	0.75	0.75	2.4	2
Sal	36	Tabes, questionable syphilitic hepatitis	8	14	0.5	1.1			1.6	1
Average	48		13.6	23.22	0.65	1.17	0.69	0.16	2.71	2

ance time and decreased dye output was due to common duct obstruction. Naturally, one gathers no information as to the functional capacity of the liver in such cases. In another case the lessened dye extraction was due, at least in part, to a grossly distorted duodenum from adhesions. A case of tabes had a dye output of only 1.6 mg. in one hour. This man had a four plus Wassermann and a questionable syphilitic hepatitis. Thirteen and six-tenths minutes was the average

first appearance time for this group as compared with 8.6 minutes in the normal group. The average maximum appearance time was 11.6 minutes in the normal group as compared to the 23.22 minutes in this group. The average dye output was 2.71 mg as compared with 22.4 mg.

*Table 5*—This table shows at a glance the hourly excretions. There was so much individual variation in the half hourly output, that we feel it is of little clinical significance. In each group, however, the average output for the first hour was greatly in excess of that for the second hour. In certain individual instances in both normal and pathologic subjects, the second hour's output was in excess of that

TABLE 5—COMPARISON BETWEEN FIRST AND SECOND HOUR OUTPUTS OF THE FOUR GROUPS

Group	Number of Cases	Output, Mg	First Hour Average, Mg	Second Hour Average, Mg
1	15	19 up	13.15	8.96
2	17	10.19	8.97	4.05
3	8	5.10	4.23	2.57
4	10	Under 5	1.82	0.85

TABLE 6—COMPARISON BETWEEN THE APPEARANCE TIME OF THE DYE AND THE QUANTITATIVE EXCRETION OF DYE IN TWO HOURS

Group	Number of Cases	Average Excretion for Group, Mg	Average First Appearance Time of Dye, Min	Average Maximum Color Time, Min	Extremes in First Appearance Time in Each Group, Min	Extremes in Appearance Time of Maximum Color in Each Group, Min
1	15	22.4	8.6	11.6	5 to 11	8.7 to 15
2	17	12.79	11.2	14.8	7 to 25	10 to 26
3	8	6.96	9.87	15.75	7 to 12	11 to 24.5
4	10	2.71	13.6	23.22	8 to 24.5	14 to 34

for the first hour. McNeil's observation that in diseased livers the greatest output of dye occurred in the second hour is not confirmed by this investigation. A great many more pathologic livers will have to be studied before any definite conclusion can be reached.

*Table 6*—Here we have tabulated the average dye output and appearance time for each group. In a general way, the smaller the amount of dye excreted, the slower it is in making its appearance. At least, this is true for the appearance of the maximum intensity of color. The latter appears to be of more significance than the time of the appearance of the first faint pink color. It will be noticed that in Group 2 the dye is slower in making its appearance than in Group 3, whereas the dye output in Group 2 is twice that in Group 3. This is not true of the appearance time of the maximum color. The maximum color

is twice as long in making its appearance in Group 4 as it is in Group 1, whereas the difference is not nearly as marked in the first appearance time. We have tabulated the minimum and maximum figures of appearance time in each group (Table 6). It will be noticed that the range of variation is extensive. For this reason we believe the time of appearance of the dye is of less importance than the estimation of the quantitative output over the period of two hours. The average dye output in Group 4 is less than one eighth of the output in the normal group, whereas the average maximum color appearance time in Group 4 is only twice as great as the normal figure. Considerable variation in the appearance time obviously may depend on the personal equation of the observer as well as upon technical difficulties, such as the temporary plugging of the tube with mucus. For these reasons we believe that the quantitative estimation of the dye output is of more significance than merely recording the appearance time.

In considering the value of estimating the quantitative output of dye when obtained through the duodenal tube, the question arises as to how much comes out through the tube and what quantity passes on down through the bowel. With the patient in the recumbent position, either on the right side or the back (preferably the right side) the second or descending portion of the duodenum is the most dorsal part of the gut. As pointed out by Knight, it constitutes a U-shaped trap, with the second part of the duodenum at the bottom of the U. It is this portion of the intestine which fills rapidly but empties slowly. Into this portion, about four inches from the pylorus, the bile empties. The tip of the tube should be passed down to a point twenty-seven inches from the lips. If the tube is passed to this point it will rest in the U-shaped trap. Care should be taken to keep the tube in this position throughout the examination. The amount of dye and bile obtained in normal individuals with thoroughly patent duct systems was found to be so nearly constant that we feel the quantitative estimation of the dye output is of decided importance.

#### CONCLUSIONS

1 We have presented here a technic in detail which it is believed will yield information of decided value concerning the functional competency of the liver.

2 Owing to the fact that the duodenal tube is now being used universally, this test can be added to the armamentarium of the average clinic with ease.

3 When a larger number of cases are accumulated and our normal standards become more definite, it should be comparable to the phenol-sulphonaphthalein kidney function test, as there seems no good reason



for believing that the liver reserve is any greater than that of the kidney when these two organs are compared as to size and their relative importance in the body economy

4 In a series of fifty cases, we found that, in a general way, a delay in the appearance time of the dye was proportionate to a decrease in the output. The estimation of the dye output in two hours is of more importance than recording the appearance time, but we believe both should be considered

5 In grossly pathologic livers the appearance time of the maximum color was twice as long as that in normal cases (23.2 minutes as compared to 11.6 minutes) and the dye output averaged but one eighth of the output in normal cases (271 mg. as contrasted with 224 mg.)

6 We suspect that the output of dye in normal cases will vary with the age, the younger the subject, the greater the amount of dye which should be covered

7 Lastly, and most important, we believe that in this test we have a method of learning something of the functional capacity of the liver when it is but slightly disturbed and when it is clinically negative to other methods of examination. It is in this group of cases particularly that the estimation of the quantitative two hour output will be of more assistance than that of the appearance time of the dye

# THE HEART IN DIPHTHERIA

## A CLINICAL AND PATHOLOGIC STUDY \*

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Cardiac failure has long been recognized as a cause of death in diphtheria. It is the factors which produce this death and the mechanism of the process that have caused dispute and discussion. Cardiac failure has been attributed by the majority of observers to an injury to the myocardium itself or its conducting system, but others have thought that the disturbance was extracardiac, that is, in the peripheral vasomotor system. On account of the various conflicting theories, it may be well to review briefly some of the opinions held respecting this very important phenomenon, before presenting our own observations.

Coghlan<sup>1</sup> believes that the diphtheria toxin acts directly on the heart muscle, resulting in certain degenerative changes, and that this is the cause of the circulatory failure. Farr<sup>2</sup> carries this conception further, expressing the view that the diphtheria toxin has a peculiar affinity for heart muscle, the extrinsic and intrinsic cardiac nerves, and the blood vessels. Fleming and Kennedy<sup>3</sup> cite a case of complete heart block in which the necropsy showed a definite myocarditis with inflammatory foci in the conducting bundle. These authors state that the case demonstrates that death in diphtheria, when the heart rate is slow and when signs of palatal paralysis are present, is not necessarily the result of inhibitory cardiac impulses.

Romberg, Passler, Bruhns and Rolly believe that early death in diphtheria is due to paralysis of the vasomotor centers in the medulla, and that late death is referable to an interstitial myocarditis. Concerning this point of early and late death, Holt<sup>4</sup> says that the explanation of heart failure during or after diphtheria is not always the same. When it occurs at the height of the disease, it is sometimes due to coronary thrombosis, probably always associated with changes in

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\* From the Department of Pathology and Bacteriology, Yale University School of Medicine

1 Coghlan, E. F. The Management of Cardiac Failure in Diphtheria, *Brit M J* 1 534, 1912

2 Farr, C. B. The Significance of Arrhythmia in Infections of Childhood, with Special Reference to Diphtheria, *Penn M J* 23 633, 1920

3 Fleming, G. B., and Kennedy, A. M. A Case of Complete Heart Block in Diphtheria, with an Account of Postmortem Findings, *Heart* 2 77, 1910

4 Holt, L. E. Diseases of Infancy and Childhood, New York, D. Appleton & Co., 1920, pp 835-1038

the myocardium. When it occurs late, and follows some sudden muscular effort or excitement without premonitory symptoms of any sort, it is probably the result of a true myocarditis. He adds, "It is by no means certain that cardiac paralysis is due to a lesion of the cardiac nerves. Toxic Myocarditis appears to be a more important factor in producing the fatal result."

Experiments made by MacCallum<sup>5</sup> on dogs, in which the influence of the vasomotors was almost entirely eliminated, tended to prove that the actual work of the diphtheria poisoned heart was fully as good as that of the normal heart. MacCallum concludes that death occurring at the height of an attack of diphtheria is not exclusively the result of direct injury to the heart, although damage to this organ may play some part in the process.

Brodie,<sup>6</sup> who sought to find the cause of early death in diphtheria, that is, death within forty-eight hours after the onset of the disease, concludes from his experiments on cats that up to a very short time before death both the blood vessels and the heart are apparently in a nearly normal condition, then there is a sudden fall in blood pressure, death following in from ten to fifteen minutes. The fall is due to the relaxation of the blood vessels, the heart continuing to beat strongly to the end. He concludes that the chief cause of death within forty-eight hours is "failure of the blood vessels, and consequent fall in blood pressure."

Price and Mackenzie<sup>7</sup> state that "cardiac paralysis" in diphtheria has long been recognized as being associated, in the majority of cases, with extensive myocarditis. Rohmer<sup>8</sup> has studied cases which show that diphtheria toxin has no special affinity for the conducting system. Tanaka<sup>9</sup> agrees that lesions of the conducting system are certainly very rarely the cause of cardiac death. Abramow<sup>10</sup> believes that subacute death is due to regressive changes in the heart muscle which come about

5 MacCallum W G. The Mechanism of the Circulatory Failure in Diphtheria, *Am J M Sc* **147** 37, 1914

6 Brodie, T G. The Physiological Action of Diphtheria Toxin, *Brit M J* **2** 128, 1899

7 Price, F W, and Mackenzie, I. Auricular Fibrillation and Heart Block in Diphtheria, *Heart* **3** 233, 1911

8 Rohmer, P. Elektrocardiographische und anatomische Untersuchungen über den Diphtherie-Herztod und dessen Beziehungen zum Reizleitungssystem, *Ztschr f exper Path und Therap* **11** 426, 1912

9 Tanaka T. Ueber die Veränderungen der Herzmuskultur, vor allem des Atrioventrikular-bundels bei Diphtherie, zugleich ein Beitrag zur Frage der Selbständigkeit des Bundels, *Virehows Arch f path Anat* **207** 115, 1912

10 Abramow, S. Pathologisch-anatomische Studien über experimentelle Diphtherie-intoxikation und Diphtherie-immunität, *Ztschr f Immunitätsforsch u exper Therap* **15** 12, 1912

from the lack of epinephrin, since under the influence of large doses of diphtheria toxin the suprarenal secretion fails

From this brief résumé it will be seen that there is by no means unanimity of opinion as to the cause of cardiac failure in diphtheria.

Although, as this résumé shows, there is great divergence of opinion as to the exact nature of the circulatory failure, there is not so much disagreement among clinicians and pathologists as to the clinical and pathological phenomena associated with the condition

Clinically, the reported cardiac findings in cases of diphtheria have been fairly uniform Flexner<sup>11</sup> in 1895, quoted figures of G Hoppe-Seyler which indicate that the percentage of cases in which the heart is affected in the course of diphtheria varies from 10 to 38 Richardson,<sup>12</sup> in an analysis of one hundred deaths from diphtheria, states that in forty per cent of the cases "myocarditis" was a complication According to Hitchcock's observations, cardiac complications were the cause of death in 15 per cent of deaths in a large epidemic of diphtheria According to Osler,<sup>13</sup> irregularity of the heart is common, being present in 60 per cent of the cases Murmurs at the apex or base of the heart are present in 94 per cent of all cases Only a relatively small percentage of cases of diphtheria show serious heart symptoms

The conditions which are regarded as serious are rapid heart action with gallop rhythm, and a drop in the pulse from 110 to 30 or 40 The physical signs include a feeble apex beat, outside the nipple line and diffuse in nature, an increase of the cardiac area to the right, to the left, or to both sides, heart sounds which are difficult to hear, murmurs, usually soft, at both apex and base, and a gallop rhythm The pulse shows great variations, it may be full and bounding, though it is usually feeble, with diminished tension S Calvin Smith<sup>14</sup> points out that the pulse abnormalities can be divided into initial tachycardia and the irregularities of convalescence Initial tachycardia is of serious import only when it persists during convalescence, and it may then be regarded as the probable precursor of heart block Fifteen per cent of the convalescent irregularities consist of high grade heart block, which is strikingly sudden in onset, death, therefore, may be expected within

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11 Flexner, S Bacteriology and Pathology of Diphtheria, Am J M Sc 109 240, 1895

12 Richardson, D L Analysis of One Hundred Deaths from Diphtheria, Rhode Island M J 3 87, 1920

13 Osler, William, and McCrae, T Principles and Practice of Medicine, 1920, p 780

14 Smith, S C Observations on the Heart in Diphtheria, J A M A 77 765 (Sept 3) 1921

thirty-six hours, none of the patients in the series of 242 patients recovered from this condition McCulloch,<sup>15</sup> from a study of eighty cases of diphtheria, concludes that in those cases in which the effect on the heart is so profound as to interfere with cardiac mechanism, the outcome is usually fatal In his study, the mortality rate was 100 per cent Dilatation of the heart is frequently described, and Hecht<sup>16</sup> who confirmed his diagnosis by the use of the roentgen ray, was able to demonstrate dilatation in the roentgenogram in 25 per cent of cases

However, it is through the interpretation of the electrocardiogram that the most definite evidence of myocardial involvement in diphtheria is being found today Almost every type of arrhythmia has been observed Hume and Clegg<sup>17</sup> have reported auricular premature beats, ventricular premature beats, paroxysmal tachycardia, auricular flutter, auricular fibrillation, heart block, nodal premature beats and reversal of nodal beats

Aviragnet and Lutembacher<sup>18</sup> maintain that the arrhythmia depends on the degree of toxic impregnation and disappears with it, but then emphasize the well known fact that tachycardia often persists for weeks and months They describe a case with complex extrasystolic arrhythmia with paroxysmal tachycardia and deranged conduction in a boy, aged 10, with ultimate recovery According to Farr, the arrhythmias which occur most commonly in diphtheria are sinus irregularity, heart block, and premature contractions He adds that in children sinus arrhythmia has no pathological significance, certainly not as regards the heart He also remarks that auricular fibrillation is not common in diphtheria, it may be temporary, though it is usually permanent and indicates serious myocardial weakness and exhaustion

From the clinical point of view, the pathologic interpretation of these arrhythmias is a matter of especial interest Do any definite lesions underly these irregularities? Blacher<sup>19</sup> says that the appearance of gallop rhythm and extrasystoles is not a direct index of the degree of anatomical damage in the myocardium, although gallop rhythm and myocarditis often occur together Coghlund believes that the presence of extrasystoles, with or without consecutive intermission of the heart's

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15 McCulloch, H Effect of Diphtheria on the Heart, *J A M A* **77** 765 (Sept 3) 1921

16 Hecht, A F Der Mechanismus der Herzaktion im Kindesalter, seine Physiologie und Pathologie, *Ergebnisse d inn Med u Kinderh* **2** 324, 413, 1913

17 Hume, W E, and Clegg, S J A Clinical and Pathological Study of the Heart in Diphtheria, *Quart J M* **8** 1, 1914-1915

18 Aviragnet, E C, and Lutembacher, R Le Coeur dans la Diphterie, *Arch d mal du coeur* **13** 1, 197, 1920

19 Blacher, W Galopprrhythmus und extrasystolen bei der diphtherischen Myokarditis, *Jahrb f Kinderh* **29** 166 1914

action, is important evidence that the heart wall is involved and that reduplication of the first sound followed by accentuation of the second is a sign of advanced myocardial disease. Aviragnet thinks that premature contractions may be provoked by slight myocardial lesions which are purely irritative. Hume and Clegg state that any form of arrhythmia of the heart, except sinus arrhythmia, indicates in diphtheria that the heart or nerves are involved in a pathological process, however mild the illness may appear. Rupe's<sup>20</sup> idea is that often lesions of the myocardium cause no clinical symptoms, but invariably the slightest lesions of the bundle produces marked clinical manifestations of conduction changes.

That lesions of the conducting tissue are not regularly present in cases of clinically demonstrable irregularity, has been demonstrated by the observations of Aviragnet, Lutembacher and LeSoudier,<sup>21</sup> and others. Furthermore, Lewis and Mathison have shown that heart block may be produced by asphyxia, and Florence Buchanan has pointed out that the phenomenon occurs physiologically in hibernating animals. There is, therefore, ample evidence to show that heart block is not necessarily due to recognized tissue changes in the node or bundle at the auriculoventricular junction.

It is seen that there is a fairly definite clinical picture of the heart in diphtheria. The pathologic findings are not so definite. The facts have been investigated, in general, through the study of (1) the myocardium, (2) the conducting system, and (3) the cardiac nerves. Investigators have described lesions in one or the other of these structures. A short summary will suffice to indicate their findings.

Aviragnet, Lutembacher and LeSoudier<sup>21</sup> have found two main types of myocardial lesions: (1) parenchymatous, and (2) interstitial and vascular. The parenchymatous changes consist in an alteration of almost all the fibers. They are swollen and vacuolated, the nuclei are pale, deformed, karyolytic, striations have disappeared, and there is more or less fragmentation. There are no fatty changes. The interstitial changes are chiefly, edema, slight leukocytic infiltration, and a small number of "infectious nodules" composed of mononuclears and fibroblasts.

Farr, in post-mortem examinations of a few cases, found foci of waxy degeneration in the bundle of His, in a case of heart block. In another case there was focal round cell infiltration of the sino-auricular

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<sup>20</sup> Rupe, W. A. The Heart in Acute Infectious Diseases, Collective Abstract, *Mod. Med.* **2** 210, 1920.

<sup>21</sup> Aviragnet, E. C., Lutembacher, R., and LeSoudier. Le Cœur dans la Diphthérie, *Arch. d. mal. du cœur* **11** 241, 1918.

node and the bundle of His. The vagi were normal. In two other cases the bundle was uninvolved, although there was a widespread myocardial degeneration. In still another case there were fatty changes and a true myocarditis, but no involvement of the bundle.

Fleming and Kennedy<sup>3</sup> described the post-mortem findings in a case of complete heart block. The heart was distinctly dilated and rather pale. A section through the auriculoventricular node and first part of the auriculoventricular bundle showed an acute inflammation with round cells, congested capillaries, a few large mononuclears and some polymorphonuclears. Similar inflammatory foci with congestion of the capillaries were found in the auricle bordering on the nodal tissues. The ventricular muscle showed evidence of an interstitial myocarditis. Briefly, the heart was the seat of a myocarditis and the auriculoventricular node and first part of the auriculoventricular bundle were involved in the inflammatory process. Both vagi were examined and found normal.

Hecht describes the anatomic changes in the heart as consisting of fatty degeneration, cloudy swelling, and interstitial round cell infiltration.

Hume and Clegg stained the auricular muscle with Sudan III and demonstrated an excess of fat, but the amount was not comparable to that in the ventricular muscle. Occasional small hemorrhages were seen. The ventricular wall contained a very large quantity of fat which was diffused throughout the muscle of both ventricles, nearly every fiber contained some droplets. In some fibers it occurred as fine granules, in others as large round globules. The smallest capillaries were dilated and engorged. The sino-auricular node showed increased vascularity and actual hemorrhage, and increased infiltration with lymphocytic cells. The auriculoventricular node and bundle of His showed engorged and dilated capillaries.

Nuzum<sup>22</sup> described an eosinophylous myocarditis in seven out of twenty-nine cases of diphtheria, which was not present in many cases of death from various acute infectious diseases.

Osler<sup>13</sup> described fatty degeneration in a majority of cases, pointing out that it may precede the more advanced degeneration in which the sarcous elements become swollen and converted into hyaline masses.

In Price and McKenzie's<sup>7</sup> case of auricular fibrillation and heart block in diphtheria, the heart grossly was soft and flabby, the ventricular chambers greatly distended. The histologic findings may be summarized as extreme degeneration, cellular infiltration of the cardiac muscle, especially in the ventricle, and in scattered foci of unequal size dis-

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<sup>22</sup> Nuzum, F. Eosinophylous Myocarditis in Diphtheria, J. A. M. A. 73 1925 (Dec. 20) 1919

tributed largely in the course of the vessels. These changes did not involve the sino-auricular node or bundle. There was no evidence of change in the nerve trunks and ganglion masses in the posterior walls of the auricle. They comment that no definite anatomical lesions have been found to be characteristic of auricular fibrillation.

Tanaka<sup>9</sup> reports that of fifteen subjects dying in cardiac syncope, fatty degeneration was present in fourteen. Interstitial infiltration with polynuclear and mononuclear leukocytes and eosinophils were observed in six of these cases. Fragmentation of the muscle fibers was observed only once. Heilbecker found similar cellular changes. D'Espine and Mallet described parietal thrombi in both auricular and ventricular walls, as well as a parenchymatous myocarditis in a case of diphtheria dying in cardiac syncope. Hume says that the nearest approach to a lesion of the auriculoventricular node or bundle found at necropsy was a slight increase in vascularity.

Councilman, Mallory and Pearce<sup>23</sup> give an excellent summary of the pathologic changes in the heart associated with diphtheria. The following is a summary of their report:

1 Degeneration of the myocardium is one of the most common conditions found in diphtheria.

2 The simplest form of this is fatty degeneration, which is found in the majority of cases. This varies in extent, at times affecting the myocardium generally, at times occurring in foci. It may appear as fine granules at the junction of the transverse and longitudinal striations, or large globules involving the greater part of the substance of the muscle cell. Fatty degeneration accompanies and seems to precede the more advanced forms of degeneration which lead to the complete destruction of the muscle. Sarcous elements become broken and change to hyaline, or large vacuoles are formed.

3 Fragmentation and fractional degeneration of the muscle are often found, but segmentation or separation of the cells along the lines of junction does not take place, or is very limited.

4 Simple fatty degeneration is found in the severe cases of short duration, the more extensive degeneration in more prolonged cases.

5 Degeneration may be so extensive as to account fully for the impairment of the heart action.

6 Acute interstitial lesions of two sorts are found:

(a) Focal collections of plasma and lymphoid cells in the tissue, accompanied by degeneration of the myocardium but not dependent on it.

(b) Interstitial changes consisting of proliferation of the cells of the tissue, which is secondary to the degeneration of the muscle. This may lead to extensive formation of connective tissue, and some of the cases of fibrous myocarditis may be due to this.

7 Thrombosis is not an uncommon condition, due to primary necrosis of the endocardium. Lesions of the vessels of the heart play but little part.

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23 Councilman, W. T., Mallory, F. B., and Pearce, R. M. A Study of the Bacteriology and Pathology of 220 Fatal Cases of Diphtheria, *J. Boston Soc. M.* Se 1 137, 1901.



Our own studies on the heart in diphtheria have consisted chiefly of (1) investigations of human cases coming to necropsy, and (2) observations on the effects of diphtheria toxin on the guinea-pig heart

The human material studied was obtained from cases occurring in the New Haven Hospital from 1917 to 1922, inclusive. During these years there were approximately 425 cases of diphtheria in the hospital. Of the total number, sixty-five patients, or 15 per cent, died. Of the sixty-five fatalities, nineteen, or 29 per cent, came to necropsy, and it is from these that the data to be described were obtained. The case histories and pathologic sections were critically studied in each case.

The diagnosis of myocarditis as a cause of death was made clinically in three cases out of seventeen, while endocarditis as an anatomic diagnosis was made in only two cases. With one exception, the patients were all children, the average age being 3.6 years. On this point it may be said that Richardson finds the greatest number of deaths under 5 years, while Osler states that in New York, from 1891 to 1900, 80.9 per cent of the deaths were in children under 5 years.

The average day of illness on admission of these seventeen patients was 5.8 days. Antitoxin was given in fifteen out of the seventeen cases in amounts varying from 4,000 to 50,000 units, in but a single case given before the day of admission. The average duration of illness was 10.8 days. It may be recalled that Osler says that heart symptoms are more common in the second or third week of the disease, and that fatal dilatation of the heart may occur as late as the sixth or seventh week. Farr thinks that cardiovascular symptoms in diphtheria occur principally at two periods (1) early, at the end of the first fortnight when the local lesions (membrane, etc.) are characteristic and just coincident or preceding the palsies, and (2) late, i. e., in the midst of convalescence (third or fourth week or later).

The physical examination of the heart in these seventeen cases revealed enlargement of the heart to percussion in four cases. The heart sounds were reported feeble in four cases. Three instances of arrhythmia were observed, a sinus irregularity not respiratory (in a patient of 42), an atypical gallop rhythm, and a typical gallop rhythm.

The gross pathologic finding showed dilatation of the right side of the heart in seven cases. This was marked, however, in only one instance. In sixteen of the seventeen cases a terminal bronchopneumonia was found. In six cases there was a fibrinous pleurisy, and in three, an acute cervical lymphadenitis.

The heart was examined histologically in all cases. From one to five sections from each left ventricle was practically the only material available in the first fourteen cases. Very few pathologic changes were found. The analysis of the necropsy findings shows that (1)

in no case was there a definite myocarditis, that is, a true inflammatory lesion, (2) the pathologic findings were more or less cloudy swelling and fat accumulation, and slight increase in the number of interstitial cells, being mostly mononuclears

In view of the fact that there was so little abnormality found, it was thought advisable to study, by way of comparison, the heart in a group of cases in which death occurred from some infection other than diphtheria. There were selected for this purpose three cases of cerebrospinal meningitis, one case of scarlet fever, four cases of bronchopneumonia and six cases of measles

One section from the left ventricle of each case was the only material available. In three cerebrospinal meningitis cases the heart was practically normal. In the bronchopneumonia group there was one case in which there was a definite focal myocarditis with mononuclear and polymorphonuclear infiltration, and another case showing an increased number of mononuclear cells in the cardiac septa. The measles group showed only a slight increase in cellular reaction in the interstitial tissue of the heart. In brief it was found that the myocardium in infections other than diphtheria shows a slight increase in cellular elements in the interstitial tissue, with, however, no definite acute inflammatory reaction.

For further investigation the heart was studied in a third group of cases in which the organ was presumably normal. All were noninfectious cases. These were difficult to obtain because in children the great majority of deaths are due to infection. One section of the heart from each of these cases was studied. The tissue in some showed a slight increase in the number of interstitial cells, no instance of a definite inflammatory reaction was encountered.

A comparison of the three groups of cases studied, diphtheria, other infections, and "normal" heart, respectively, shows that the differences are quantitative rather than qualitative. There is no sharp line between the normal and the abnormal, and no clear cut difference can be detected in the hearts from diphtheria cases and those from other types of infections. In other words, the pathologic study of this material indicates that the lesion in the myocardium in diphtheria is not specific.

The first fourteen cases cited above furnished material which was somewhat incomplete as respects both clinical and pathologic data. Opportunity, however, was afforded to make a more intensive study of three additional cases which came to necropsy during the last six months.

One case is an excellent example of a myocardial death in diphtheria, diagnosed as acute myocarditis clinically and showing a striking myocarditis pathologically. The following is a brief summary of the case.

## REPORT OF CASE

T G (Hospital No 3891), aged 7 years, was admitted Dec 20, 1921

*Complaint*—Diphtheria

*Family History*—Family living and well Mother, living and well Pregnancies, four normal, no miscarriages No history of tuberculosis

*Past History*—Full term, normal delivery, breast fed, development normal, always had a deformed chest Acute infections pertussis, uncomplicated Had vomiting attacks about every four months, mother gives castor oil and attacks subside.

*Present Illness*—Onset seven days ago (Dec 14, 1921) Vomiting attack, mother gave castor oil which did not help very much Vomited next day also, especially after meals Two days later (December 16) the child complained of sore throat and mother noticed that night a swelling in the neck A doctor was called the next day, he made a diagnosis of diphtheria and gave 10,000 units of antitoxin Glandular swelling did not subside although the child improved Cultures were positive

*Physical Examination*—GENERAL Child not prostrated, face flushed, lips red, breathing quiet Head normal in size and shape, depression in region of anterior fontanel Pupils equal and react to light and accommodation, extra-ocular movements normal, conjunctivae of good color Nose Evidence of epistaxis, no discharge Ears No discharge, drums normal Mouth Teeth carious and incisors notched Tongue Clear, papillae not prominent, red at tip, buccal mucosae clear, pharynx, red, grayish white membrane over both tonsils and extending up on soft palate to side of uvula Glands At angles of jaws glands are swollen and tender, axillaries palpable, right epitrochlear gland very small and just palpable Chest Extraordinary appearance, left side of chest is very much deformed and thinned so that the heart is visible and palpable, pulsating very superficially under a thin wall, sternum is elevated and forms a crest Lungs Clear Heart Apex not made out and borders not at all clear, visible pulsation seen at base of heart, no thrill palpable, loud systolic bruit heard, localized at base, rate not rapid, sounds of good quality and regular Abdomen Spleen not felt, liver at costal margin, no masses or tenderness Genitals Left testicle undescended Reflexes Active and equal

*Diagnosis*—Diphtheria, pharyngeal, depression of chest

*Course*—By December 23, the throat was only slightly reddened Tonsils enlarged but exudate all gone Lymph nodes at angle of jaw still swollen and tender

December 24, heart showed gallop rhythm and was at times irregular Liver, tender, one and one-half finger breadths below costal margin Lungs, clear Later on same day child became worse Complained of pain in the abdomen Abdomen rigid, especially in right upper quadrant Heart weak, gallop rhythm, pulse feeble Face has anxious expression Night of December 24, rapid breathing, lips cyanotic, face pale, liver edge at level of umbilicus Pulse became impalpable Heart irregular and of feeble quality Patient died suddenly after raising his head from the pillow

*Clinical Diagnosis*—Pharyngitis, diphtheritic, myocarditis, acute toxic

Temperature December 20, 99.8 F, December 21, 101.0 F, December 24, 98.6 F

Respiration 20

Pulse December 20, 110, December 23, 80, December 24, 96

Hemoglobin, 75 per cent, red blood cells, 4,820,000, white blood cells, 14,400, December 20, 53,000 December 24

Urine albumin, 0.5 gm per liter December 24 (slightest possible trace December 20)

*Pathologic Findings*—(Necropsy 579) Gross Body length, 154 cm, weight, 16 kilos, weight of heart, 120 gm

A small milky patch is found on the anterior surface of the right ventricle. In the right auricle is an inelastic friable blood clot attached to the muscular pectinati. The right ventricle is dilated. The left ventricular cavity is slightly dilated. The heart muscle is homogeneous pale brown in color.

*MICROSCOPIC* Blocks were taken from the right auricle, interauricular septum, left ventricle, middle, left ventricle, apex, interventricular septum, and right ventricle. (Paraffin sections were stained with hematoxylin and eosin, frozen sections were stained with Sudan III for fat.)

*Hematoxylin-Eosin Sections* There is a striking change in the heart muscle. (1) The muscle fibers appear degenerated in areas. The protoplasm is homogeneous or is absent, mere strands of tissue being left. There is actual necrosis of muscle fibers in which the nuclei have disappeared. Many of the muscle bands are widely separated. (2) There is a marked mononuclear cell infiltration, the cells occurring in foci. Among them may be seen eosinophils. Some of these foci include over a hundred cells and separate the muscle fibers widely. (3) There are some red blood cells free among the fibers. (4) Strands of fibroblasts are seen between the muscle fibers.

The changes were most clear-cut in the left ventricle but were observed in all parts of the heart studied. The interauricular septum showed in addition several areas of hemorrhage. The right auricle contained a thrombus. The accompanying illustration shows these changes very well.

*Fat Stains* Throughout the whole there is a marked fatty infiltration. The fat is focal in distribution and these foci are scattered throughout the myocardium. The droplets or granules fill the cytoplasm of the muscle elements. Each focus consists of a number of muscle fibers. The left side of the heart is more affected than the right and the interventricular septum more than the outer walls.

*CASE 2*—H. A. (Hospital No. 1787), aged 2½ years, entered the hospital Aug. 18, 1921.

*Complaint*—"Can't breathe."

*Family History*—Father has cough, possibly tuberculous, father's sister is in a tuberculosis sanitarium, mother, living and well. Pregnancies five normal, no miscarriages.

*Past History*—Full term, normal delivery, breast fed for three months. Screams out in sleep. Eyes filled with pus in morning. Attacks of croup. Has numerous earaches. No history of any acute infection. Has had intestinal worms for about five months.

*Present Illness*—The onset was twenty-four hours before admission. The patient awoke from an afternoon nap with difficulty in breathing. He became steadily worse and at night became very restless, had deep labored breathing, voice hoarse. Had fever and refused food. Became worse, doctor saw him the next afternoon and said he had diphtheria and sent him to the hospital.

*Physical Examination*—*GENERAL* The child presented a striking picture, with difficult breathing, anxious expression, face flushed with pallor about the mouth, body surface temperature considerably raised. Lymph Glands Palpable at angle of jaw. Face. Some suggestion of facial weakness on right. Lips. Slightly cyanosed. Throat. Pharynx considerably injected, tonsils slightly enlarged and injected, post-pharyngeal wall injected, over lower pole of right tonsil is a small, white patch of exudate. Larynx. Voice is hoarse and barely audible, cough whistling and dry. Chest. Well formed and symmetrical, on inspiration there is a considerable retraction of the suprasternal notch, also of the interspaces, and the lower ribs and costal margins sink in at each inspiration, retraction of the xiphoid. Lungs. Respirations rapid and labored, coarse, moist râles, laryngeal in character, heard over whole

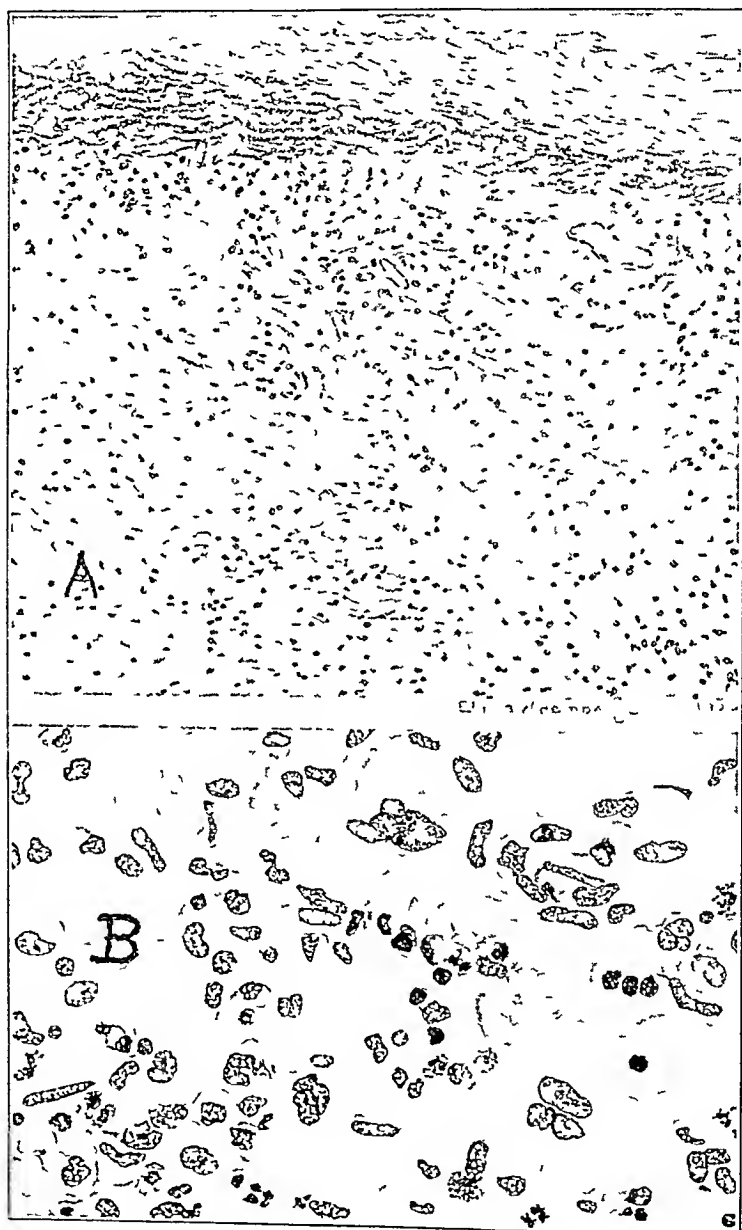
chest Heart Not enlarged, rate very rapid, heart sounds clear, no shocks, thrills or murmurs

*Diagnosis*—Diphtheria, laryngeal

*Course*—August 18 Intubation

August 19 Breathing more difficult

August 22 Whooping cough noted



Acute myocarditis in a case of fatal diphtheria (Necropsy 579) *A*, low power *B*, high power

August 25 Laryngeal stridor

August 27 Bronchopneumonia

September 1 Suddenly became worse, pulse could not be counted, dyspnea; tracheotomy done, convulsions followed by death

*Final Diagnosis* — Laryngeal diphtheria, pertussis, bronchopneumonia, chronic ulcerative laryngitis, ascaris lumbricoides infection Temperature, from 108 to 98.8 F Respiration, from 24 to 88 Pulse, from 112 to 190 per minute Hemoglobin, 85 per cent, red blood cells, 4,950,000, white blood cells, 27,000

*Pathologic Findings* — (Necropsy 540) GROSS Length, 82 cm, weight, 11.3 kilos, weight of heart, 60 gm The right auricle and ventricle are moderately dilated The auricle contains an elastic clot

MICROSCOPIC Blocks were taken from the right auricle, interauricular septum, left ventricle, middle, left ventricle, apex, interventricular septum, and right ventricle (Paraffin sections were stained with hematoxylin and eosin, frozen sections were stained with Sudan III for fat)

Hematoxylin-Eosin Sections The muscle fibers appear normal in all the sections studied A few of the blood vessels are congested and there are several small foci of mononuclear infiltration A few fibroblasts are seen here and there

Fat Stains There is practically no fat seen in any part of the heart muscle which was studied

CASE 3—S W (Hospital No 2409), aged 7½ years, entered July 27, 1921

*Complaint*—Difficulty in breathing

*Present Illness*—Onset one day before admission Difficulty in breathing which grew worse Had slight cough

*Physical Examination* — Marked retraction of ribs with inspiratory and expiratory difficulty Marked drawing in of episternal notch during inspiration Membrane on tonsils

*Course*—Difficulty in breathing with retraction continued in spite of intubation He became cyanotic, heart slightly irregular Tracheotomy done and cast of membrane 2.5 cm long and 0.5 cm in thickness was removed from the trachea Obstruction below the tube became so marked that in spite of surgical treatment, respiration ceased

*Diagnosis* — Diphtheria, pharyngeal, laryngeal and tracheal, bronchopneumonia

Temperature, from 100 to 104 F Respiration, from 40 to 60 per minute Pulse, 146 to 160 per minute Hemoglobin, 80 per cent, red blood cells 5,120,000, white blood cells, 18,000

*Pathologic Findings* (Necropsy 516) — GROSS Length, 85 cm, weight of body, 18.2 kilos, weight of heart, 60 gm

There was very little subepicardial fat The chambers of the heart showed slight dilatation The endocardium was a homogeneous dark red

MICROSCOPIC Blocks were taken from the right auricle, interauricular septum, left ventricle, middle, left ventricle, apex, interventricular septum, and right ventricle

Hematoxylin-Eosin Sections The heart muscle fibers appear fairly normal throughout the sections There are mononuclear cells scattered here and there but there are no definite foci of these cells

Fat Stains There is no fat present in any part of the heart studied

*Comment*—It will be seen that only the first of these three cases represents a typical acute clinical myocarditis of diphtheria, and that anatomically this finding is borne out by the presence of a striking acute myocarditis with characteristics as described above

The second case did not show a myocardial change either clinically or anatomically

The third case did not show a myocarditis clinically, but did show a mild myocardial involvement pathologically

As the fat changes were so striking in the case of typical acute myocarditis, two relatively normal hearts of about the same age were stained for fat to study their content

1 D DeL, aged 3 years (Hospital No 1478, Necropsy 518), died of fibrosarcoma of nasopharynx. The heart showed no fat in the muscle fibers

2 E O, aged 6 years (Hospital No 3698, Necropsy 203), died of glioma of brain. The heart showed no fat in the muscle fibers

In order to see if a myocarditis might be produced experimentally by diphtheria toxin, four guinea-pigs were injected with the toxin. The table shows dosage, length of life, etc

SUMMARY OF DATA OF GUINEA-PIG EXPERIMENTS

Guinea Pig No	Weight in Gm	First Date	Initial Dose*	Subsequent Dosage, Fourth day	Died	Lived, Days
1	425	7/26/21	1 cc of 1:300	1 cc of 1:150	7/30/21	5
2	425	7/26/21	1 cc of 1:300	1 cc of 1:150	8/ 1/21	7
3	400	7/26/21	0.5 cc of 1:300	1 cc of 1:150	8/ 2/21	8
4	400	7/26/21	0.5 cc of 1:300	1 cc of 1:150	8/ 6/21	12

\* The diphtheria toxin was obtained from the New York City Board of Health, M L D equals 1/1000 cc for guinea pig

In order to simulate the gradual progressive action of diphtheria toxin in the human, it was decided not to inject immediately the M L D, but to give less at the first injection. This was done, and the first two guinea-pigs were injected intramuscularly with 1 cc of 1:300, and the second two with 0.5 of 1:300, respectively. As all the animals were living on the fourth day, they were each injected with 1 cc of 1:150 toxin.

The first animal died on the fifth day, the next on the seventh, and the last two on the eighth and twelfth days, respectively.

The hearts in each case were studied pathologically, hematoxylin and eosin stains and Sudan III for fat being made. They showed

*Guinea-Pig 1*—Hematoxylin and Eosin Stain. The muscle fibers appear somewhat cooked. There are red cells scattered free between the muscle fibers usually appearing singly. There are a few young fibroblasts in strands seen between the muscle fibers. The heart is very vascular.

*Sudan III*. There is a marked deposit of fat in the muscle fibers. This is focal in nature, appearing especially around the nuclei and involving a large number of muscle fibers. The fat accumulation seems to be more marked in the inner portion of the heart wall, that is in the subendocardial zone.

*Guinea-Pig 2*—Hematoxylin and Eosin Stain. The muscle fibers have a somewhat cooked appearance. There are a few foci of large mononuclear cells. The blood vessels of the myocardium are not so conspicuous as in Guinea-Pig 1.

*Sudan III*. The fatty infiltration is marked. There are large foci of fat throughout the heart and many fibers are involved. In this case the fat appears to be nearer the outer than the inner wall of the heart.

*Guinea-Pig 3*—Hematoxylin and Eosin Stain The muscle fibers appear to be somewhat thinned out No mononuclear cell accumulations are seen

Sudan III There is practically no fat seen in the muscle fibers

*Guinea-Pig 4*—Hematoxylin and Eosin Stain The heart muscle appears somewhat cooked Capillaries are conspicuously congested

Sudan III There is practically no fatty infiltration of the heart muscle fibers

A study of the hearts of two healthy guinea-pigs was made to determine the character of the normal myocardium and its fat content

*Normal A*—Hematoxylin and Eosin Stain The heart muscle fibers appear normal The blood vessels are numerous There are a few areas of mononuclear infiltration, especially perivascular There are also some large mononuclear cells between the muscle fibers

Sudan III There is no fatty infiltration

*Normal B*—Hematoxylin and Eosin Stain The heart muscle appears normal The blood vessels are numerous There are a few areas of mononuclear infiltration around the blood vessels and between the muscle fibers The heart is essentially like that of Normal A

Sudan III There is no fatty infiltration

It will be seen that the first two guinea-pigs which received the larger initial dose and which died first, showed marked fatty infiltration The distribution and character of the fat corresponds exactly to that found in the human heart in the first case cited, although the myocardium does not show the focal necrosis of the fibers and cellular infiltration so marked in that case

These experiments, we believe, are sufficient to show that while diphtheria toxin does damage the heart as evidenced by a pronounced focal fat accumulation in the fibers, it does not, even in fatal doses resulting in delayed deaths, bring about a true myocarditis In this respect the findings agree with those in the majority of fatal cases of human diphtheria

#### SUMMARY

1 Clinical evidence indicates that a large proportion of the fatalities in diphtheria are due to circulatory failure (Herztod)

2 Death in these cases is probably referable to injury to the myocardium itself or its conducting system, although experimental evidence (MacCallum) points to a serious disturbance in the peripheral vasomotor system

3 A definite inflammatory reaction (true myocarditis) is only exceptionally demonstrable at necropsy (one out of nineteen cases in the present series) Fat accumulation and cloudy swelling are very regularly seen, but are not more pronounced than in other acute infectious diseases such as scarlet fever, measles, and pneumonia In other words, no specific myocardial lesion has been demonstrated



4 The injection of lethal or sublethal doses of diphtheria toxin in guinea-pigs produces degenerative changes in the heart muscle similar to those seen in the human heart in fatal diphtheria, but such injections do not induce a true inflammatory reaction<sup>24</sup>

24 The following references also bear on this subject

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# THE PRODUCTION OF ATHEROSCLEROSIS IN RABBITS BY FEEDING DIETS RICH IN MEAT

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In an earlier communication Newburgh and Squier<sup>1</sup> reported the occurrence of atherosclerosis in two small groups of rabbits (eleven in all) that had been fed high protein diets. While the evidence at hand indicated that the vascular lesions had been caused by the high protein diets, such a conclusion was not safe because it was felt that the experiments were too few to permit a generalization.

This paper deals with the further investigation of the effect of high protein diets on the arteries of rabbits, but the presentation of the new material will be preceded by a definition of the term "atherosclerosis," and by a discussion of the work of earlier students of experimental atherosclerosis.

## DEFINITION

The causes of human atherosclerosis have been sought for, by means of animal experimentation, by a large number of investigators. They have attempted to injure the vessels by the use of a great many different procedures, and a variety of vascular lesions have been reported. But much of the work, and more especially the earlier studies, have not contributed to the understanding of the problem since so often the lesion obtained in the experimental animals was in no sense the analogue of the human disease. The investigator must, by the use of the agent which he suspects of being a cause of human atherosclerosis, produce in animals a picture which at least closely resembles what is found in the human being before he can with justification claim that this agent may be a cause of human atherosclerosis.

The term atherosclerosis as used in dealing with the diseases of arteries occurring in human beings, is intended to designate a primary lesion of the intima, and to exclude lesions of the intima which result from disease of the media or vasa vasorum. The process presents itself to the naked eye, in its most characteristic stage, in the form of discrete or confluent, slightly raised, pale yellow, opaque plaques and streaks. This earlier form of the lesion may later be altered by softening of the contents of the nodule and the loss by ulceration of the caseous material thus formed. The deposition of calcium salts in

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\* From the Department of Internal Medicine, Medical School University of Michigan.

1 Newburgh and Squier. *Arch. Int. Med.* 26:38 (July) 1920.

large amounts converts the base of the ulcer into a hard but brittle depression. But these well recognized gross appearances are not always sufficient to permit the observer to distinguish between primary atherosclerosis and other vascular lesions which affect the intima secondarily—in particular syphilis of the aorta, and in experimental work, the microscopic features should be used in reaching a decision. The histologic picture presented by this primary disease of the intima depends on the stage at which it is seen.

The initial lesion consists essentially of a necrosis or fatty degenerative change in the endothelium or the fibroreticular cells of the intima. The yellow elastic fibers are separated and pushed apart by the swollen fatty cells. With increasing injury the elastic fibers undergo a granular degeneration and break up into a granular detritus.

Following the stage of primary injury, a regenerative compensatory fibrosis occurs with the production of new elastic fibers. The growth of new elastic fibers is often marked and usually occurs chiefly on the lumen side of the lesion so that the degenerated area comes to appear to be located nearer to the media than to the lumen.

A secondary degeneration of this sclerotic area occurs and may result in rupture of the atheromatous patch into the lumen of the vessel, forming the so-called atheromatous ulcer. In advancing lesions there is a progressive fatty degenerative change involving not only the intima but extending into the interlamellar fibroreticulum of the media. At any time calcification may be an added factor. The two processes, the degenerative and the regenerative-compensatory, go hand in hand and in old progressive cases may lead to the most marked changes of the vessel wall extending even to the adventitia.

When one wishes to determine whether an experimental vascular lesion is atherosclerotic in type, it is always desirable to examine the earlier stages of the lesion. In primary disease of the intima it will be noted that this coat has undergone great thickening and that its increased width is chiefly due to the presence in it of large cells loaded with fat imbedded in a hyperplastic elastic tissue. The coexistence of the enormous amounts of fat and the hyperplasia of the elastic tissue stamp the lesion in question as a true primary disease of intima—an atherosclerosis.

#### LITERATURE

Failure to use these generally accepted criteria as a basis for determining whether any given lesion could properly be considered atherosclerotic has given rise to much confusion. Thus Saltykow,<sup>2</sup> in his review of the literature published in 1908, was compelled to point out

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<sup>2</sup> Saltykow. *Centralbl f Allg Path* 19 321, 1908.

that very little of the experimental work up to that date bore on the problem of the cause of human atherosclerosis since the lesions obtained in the animals did not resemble the human type. The use of mechanical methods, the injury of nerves, the injection of alcohol, lead and epinephrin did not cause vascular disease which resembled human atherosclerosis.

*Epinephrin*—But the experiments with epinephrin, even though they failed to produce primary intimal disease, must, nevertheless, be given serious consideration since the injection of epinephrin causes a type of vascular lesion which is frequently seen in man and which by a few writers is included under the heading of atherosclerosis. Monckeberg<sup>3</sup> showed that this lesion, characterized by necrosis and calcification of the media, is a pathologic entity, originating in and often restricted to the media, and clearly separable from the primary intimal disease. Monckeberg pointed out that the calcification of the media was first recognized by Virchow and separated by him from "atheroma" (disease of the intima). Some writers have expressed the belief that calcification of the media and atherosclerosis were both responses to a common etiologic factor. In support of this belief, they point out that the peripheral vessels in which calcification is most often found possess thick muscular walls, whereas, the aorta and other central arteries have relatively little muscle in their walls. They assume that these differences are sufficient to cause the reaction to an insult to take place in the media when the vessel is thick walled and in the intima when it is thin walled. But Monckeberg showed that this hypothesis did not conform to the facts, for primary intimal changes are frequently seen in vessels of the muscular type, medial calcification occurs in the central arteries, often both lesions occur in the same artery. He concluded that medial calcification cannot be the anatomic equivalent of the intimal disease of the aorta. It is important to make this distinction between true atherosclerosis and calcification of the media since it is only on this basis that a proper evaluation of the epinephrin work can be made. The intravenous injection of epinephrin into rabbits produces lesions which are identical with the Monckeberg type of human vascular disease. Josué,<sup>4</sup> who was the first to study the effect of epinephrin on the vessel wall, announced in 1903 that he had obtained "atheroma" of the rabbit's aorta. His statement, however, was based only on the macroscopic appearance of the vessel. Subsequently he agreed with later workers that the lesion was primarily medial. The radical differences between the epinephrin changes in the rabbit's aorta and human atherosclerosis are well sum-

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3 Manckeberg Arch f path Anat **216** 408, 1914

4 Josue cited by Saltykow<sup>2</sup>

marized by Saltykow, as follows "In man the disease is localized in the intima, in the rabbit in the media. In man the lesion shows a high grade fatty degeneration, in the rabbit little or no fat is seen. In man calcification occurs as the end stage of the degenerative process, in the rabbit it appears at the beginning of the disease." But in spite of these basic differences, some experimentors have nevertheless maintained that the epinephrin lesions of rabbits were the analogue of human atherosclerosis, on the ground that epinephrin attacks the media in the rabbit's aorta because the latter is thick walled, whereas the thinness of the media in the human aorta forces the lesion into the intima. This argument is very similar to the one used by writers on human pathology who tried to show that medial calcification of the peripheral arteries is the anatomic equivalent of true atherosclerosis. The unsoundness of this argument was, as already noted, shown by Monckeberg. Such reasoning becomes quite untenable in the light of two facts: (1) widespread and advanced disease of the intima of the rabbit's aorta, the counterpart grossly and microscopically of the human disease of the intima, may be produced by suitable methods. Saltykow<sup>5</sup> and Klotz<sup>6</sup> have produced atherosclerosis in rabbits by injection of bacteria. Ignatowski,<sup>7</sup> Steinbiss<sup>8</sup> and we have obtained the same type of intimal disease in the rabbit by feeding abnormal diets of various sorts.<sup>2</sup> Klotz<sup>9</sup> has shown that epinephrin has a selective action on muscle. It causes necrosis of muscle whenever it comes in contact with it in sufficient concentration be it skeletal muscle, heart muscle or the smooth muscle of the media.

Epinephrin then, attacks the media of the rabbit's aorta for one reason only, namely, because the media contains muscle cells. The supposition that epinephrin produces medial calcification in the rabbit because atherosclerosis in the rabbit is by the nature of things, as is implied by some writers, a primary disease of the media, is quite untenable since, as just pointed out, primary intimal disease may be produced in the rabbit by the use of proper agents. Epinephrin fails to produce primary intimal lesions because epinephrin has no affinity for the cells of the intima. If the arteries of man are ever damaged by it, the lesions must occur in the media and produce the Monckeberg calcification of the media.

*Bacteria*—Saltykow<sup>2</sup> was accordingly quite justified in his statement in 1908 that the only method which caused, in the rabbit, vascular

5 Saltykow. Beitr. z. path. Anat. **43** 147, 1908.

6 Klotz. J. Exper. M. **12** 707, 1910.

7 Ignatowski. Arch. f. path. Anat. **198** 248, 1909.

8 Steinbiss. Arch. f. path. Anat. **212** 152, 1913.

9 Klotz. Brit. M. Jour. **2** 1767, 1906.

lesions that could be considered the analogue of human atherosclerosis was the injection of bacteria. Gilbert and Lyons (quoted by Saltykow), as early as 1889 occasionally obtained intimal lesions following the intravenous injection of an organism recovered from a patient with endocarditis. Subsequent workers reported a few positive results but more often failed to produce a lesion which resembled the human type sufficiently to justify its being called atherosclerosis. Finally Klotz,<sup>9</sup> in 1906 published experiments which showed conclusively that intimal lesions of the atherosclerotic type could be produced regularly by the intravenous injection of bacteria (typhoid bacillus and streptococcus) into rabbits. Saltykow<sup>7</sup> in 1908 reported the same type of intimal lesion following the injection of different strains of the staphylococcus.

These two groups of experiments seemed to have established beyond reasonable doubt the idea long held by students of the subject, that atherosclerosis is often caused by infection. But unsuccessful attempts of later workers to confirm these experiments reopened the whole discussion and led Saltykow to repeat his work on a more elaborate scale.

*Abnormal Diets*—Before taking up Saltykow's second paper, it is necessary to review some of the work of a group of investigators who had shown that abnormal diets could cause atherosclerosis, since Saltykow's later experiments incorporated the ideas emanating from the work with these diets. Ignatowski<sup>7</sup> fed rabbits varying amounts of meat, eggs and milk and obtained lesions of several organs, including the aorta. He stated that "all rabbits fed animal protein showed aortic lesions of the same type. They consist of confluent and single plaques, yellow, round or irregular." Stuckey<sup>10</sup> devised experiments to discover what portion of the animal diet was responsible for the lesion. For this purpose he fed four series of rabbits as follows: (1) cow's milk plus egg albumin, (2) cow's milk plus meat juice, (3) cow's milk plus egg yolk, (4) cow's milk to which egg albumin, egg yolk and meat juice was added. Only the animals of the third and fourth series that had received the egg yolk showed well marked vascular lesions. These data led him to conclude that the egg yolk was responsible for the lesion and that the protein contained in the animal diets had little to do with the vascular disease. Chalutow<sup>11</sup> had, in the meantime, studied the effect on the liver of feeding egg yolk, and had found a marked infiltration of liver cells by fatlike substances whose physical characters showed them to be rich in cholesterol. Anitschkow and Chalutow<sup>11</sup> then fed cholesterol dissolved in hot sunflower seed oil to rabbits. After a few weeks they saw an infiltration of the liver parenchyma with cholesterol.

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10 Stuckey. *Centralbl f Allg Path* **12** 379, 1911, **13** 910, 1912.

11 Chalutow. *Centralbl f Allg Path* **24** 1, 1913.

The same material was found in the aorta, spleen and all other organs examined. They believed that these experiments explained the results noted by earlier investigators who had fed abnormal diets, and that all such diets had produced lesions because they contained an excess of cholesterol. Wacker<sup>12</sup> in the same year called attention to the occurrence of atherosclerosis in rabbits to whom cholesterol mixed with oats had been fed. The animals ingested about 15 gm cholesterol daily. The cholesterol values in the blood rose slowly, and the increase in some instances was striking. The report deals with eight rabbits, five of which were fed for more than 120 days. Four of these showed aortic atherosclerotic lesions at the necropsy—widespread in three instances, but minute in one animal that had eaten the cholesterol 160 days. The rabbit that ate the cholesterol for the greatest number of days had the highest blood cholesterol value but a normal aorta.

Wacker himself pointed out that the lesions, in degree and extent, were not parallel to the amount of cholesterol fed nor to the duration of the experiment.

Saltykow<sup>13</sup> was convinced that the cholesterol contained in the animal diets had caused the vascular disease and pointed out that the aortic lesions found in the rabbits that had been injected with staphylococci by him and which had formed the basis of his report in 1908 might have been in part or wholly due to the diet, since his animals had received a considerable amount of milk. In order to decide this question, he injected various strains of staphylococci into a group of rabbits whose diet contained 100 c c of milk daily. A second group of rabbits received no treatment other than the addition to the diet of 400 c c of milk daily. He found that milk feeding caused as great changes in the aorta as the combination of milk feeding and the injection of bacteria. Furthermore, the lesions obtained in milk fed rabbits that had been injected with staphylococci were identical with the lesions seen in the animals that had received milk only. These lesions were indistinguishable from those produced by cholesterol. Even though milk contains much less cholesterol than egg yolk, Saltykow's calculations showed that the total amount of cholesterol eaten by his milk fed rabbits was greater than the amount ingested by rabbits made atherosclerotic by being fed egg yolk and this led him to conclude that the chief etiologic factor in his experiments was the milk feeding but that the staphylococci had a contributory effect on the formation of the lesion. In so doing, he assumed that often repeated small doses of cholesterol would have the same ultimate effect as fewer large doses. But such

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12 Wacker Arch f Exper Path u Pharmakol **74** 422, 1913

13 Saltykow Beitr z path Anat **57** 415, 1913-1914

an assumption is at variance with the pharmacologic principle that concentration is one of the prime factors in determining the effect which any substance will have on cells

In the absence of an actual experimental demonstration that the small amount of cholesterol present in 100 cc of milk is capable of causing vascular disease, one is surprised to find that Saltykow did not adhere to his original contention, namely, that in the rabbits receiving injections of bacteria and 100 cc milk daily, the aortic disease was caused by the bacteria

The vascular disease found in the rabbits that were fed 400 cc milk daily was presumably caused by some ingredient in the milk. But not necessarily by the cholesterol since the daily dose of it was still far below that contained in one egg. On the other hand, 400 cc milk contains approximately 15 gm protein, an amount greatly in excess of that habitually eaten by a rabbit. Subsequent work has shown that high protein diets will cause atherosclerosis in the rabbit. Hence, one is not required by the data at hand to attribute the atherosclerosis to the cholesterol in the milk.

The investigation of the effect of abnormal diets upon the arteries was continued by Steinbiss<sup>8</sup>. He fed a diet made of dried powdered horse liver (freed of fat) mixed with moistened bread. The aorta of rabbits presented small raised plaques as early as two weeks from the beginning of the experiment. Microscopic examination showed these lesions to be medial and identical with the epinephrin injury. Even in the most advanced cases, the intima as a rule, was normal and never showed more than trifling changes, which when present were not those of human intimal disease. In some animals which were fed the longest time, the aorta was normal but the media of the peripheral vessels was extensively involved. The myocardium and skeletal muscle showed the same type of lesion as the media. Saltykow<sup>12</sup> repeatedly found medial lesions of this same type in treated and in fresh animals and believed that these necroses of the media were spontaneous. Steinbiss' experiments with this diet were so few and relatively of such short duration that they, taken by themselves, are not of much value. The paucity of data was caused by the very high mortality of the animals. But this difficulty was overcome by the occasional addition of a little carrot or other green food to the liver-bread mixture. The mortality was thereby greatly reduced and the condition of the animals improved in every way. A group of rabbits kept on this modified diet from four to six months showed no vascular lesions. It is difficult to believe that the addition of a very small amount of green food to the liver-bread diet would prevent the occurrence of the medial lesions over a period of six months, if such lesions could, in fact, be



caused by the ingestion of liver without carrots for only two weeks. Of far more importance are the data which Steinbiss obtained when he fed this same diet, made up of dried liver, bread and greens, to ten rabbits for nine months. The aortas of all of these ten animals showed well marked atherosclerosis of the human type.

The experiments of Ignatowsky, Saltykow and Steinbiss must be accepted as proof that diets containing large amounts of animal food will cause atherosclerosis in the rabbit. Ignatowsky, who used meat, milk and eggs in varying combinations, attributed the occurrence of the vascular disease in his animals to the presence of animal protein in the diet. This view, however, was not accepted by Stuckey, whose investigations led him to conclude that the lipoids and not the protein must be held accountable for the vascular injury. Then followed the work with cholesterol, which was generally accepted as a satisfactory demonstration that the cholesterol in the diet was the cause of the vascular lesions reported by Ignatowsky, Saltykow and others who had fed animal diets to rabbits.

But such a conclusion was not warranted by the evidence at hand for Ignatowsky's diets were not only high in cholesterol but also in protein, and even though Stuckey, Chalатов and Anitschkow had shown that diets high in cholesterol would cause extensive atherosclerotic lesions, they had not shown that diets high in protein but poor in cholesterol would not cause similar vascular lesions.

Knack<sup>14</sup> shortly thereafter questioned whether a simple hypercholesterinemia could cause atherosclerosis, suspecting that some other agent was always responsible for the primary lesion. He pointed out that the animal diets used by his predecessors were not only high in cholesterol but were also abnormal for rabbits in other respects and might thus give rise to metabolic disturbances which had caused the primary vascular injury attributed to the hypercholesterinemia. Such criticism, however, did not apply to the feeding experiments of Chalатов and Anitschkow since they used only oats, hay and greens to which cholesterol dissolved in hot sunflower seed oil was added. Knack wondered whether products of this oil had injured the intima.

Knack did not discuss the work of Wacker who had fed cholesterol and oats. But he could properly have insisted that a diet restricted to oats is in itself abnormal, and when long continued leads to metabolic disaster. Here again, the primary vascular injury could conceivably have been caused by substances derived from the abnormal nutrition.

In this connection it is well to recall that an abundance of cholesterol is found in many inflammatory and degenerative lesions which are

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14 Knack. *Arch f path Anat* 220 36, 1915

clearly caused by local injuries. The deposition of cholesterol in them takes place long after the primary injury has occurred. The presence of cholesterol in a lesion depends upon the nature of the lesion and not upon the level of the blood cholesterol.<sup>1</sup> For example, the intimal lesions caused by the injection of bacteria into rabbits or those found in the aorta of human beings dying of typhoid fever show as much cholesterol as do the intimal lesions which occur in animals fed an excess of cholesterol, in spite of the fact that the blood in infections contains less than the normal amount of cholesterol.

Knack attempted to answer his query by feeding one group of rabbits an entirely normal diet to which he added very large amounts of cholesterol, and feeding a second group of rabbits an animal diet similar to that used by Ignatowsky. The cholesterol was enclosed in pellets of moistened bread and he was able to feed as much as 4.5 gm daily in this way. The second group was fed milk, one egg and greens daily resulting in an intake of only 0.3 gm cholesterol. The milk-egg feeding, in spite of containing much less cholesterol and not being continued so long produced a well marked atherosclerosis in every rabbit of this group. On the other hand, most of the animals that ate the large amounts of pure cholesterol showed no vascular injury. A few of them exhibited small intimal lesions. He concluded that pure cholesterol when fed with a normal diet does not cause atherosclerosis, and that the milk-egg diet did produce atherosclerosis because such a diet is accompanied by abnormal metabolic products which cause the primary vascular injury.

It would appear, then, in the light of our present knowledge, that cholesterol plays an important part in the formation of the atherosclerotic lesion, but there exists as yet no entirely satisfactory proof that simple hypercholesterinemia is a primary cause of atherosclerosis.

*Strain*—Several authors believe that they have produced atherosclerosis by subjecting the arteries to unusual strain. Klotz<sup>6</sup> suspended rabbits by the hind legs daily for three minutes for as long as 130 days. He reported the occurrence of two types of injury. In those arteries which bore the brunt of the increased pressure, the media showed degenerative changes of the type produced by epinephrin. On the other hand, some of the smaller arteries which felt the increased load less showed atheromatous changes of the intima. Harvey<sup>15</sup> raised the blood pressure of rabbits by digital compression of the aorta below the kidneys. He found changes in the aorta which were entirely analogous to those caused by the injection of epinephrin. Steinbiss<sup>8</sup> tried to duplicate the findings of Klotz and of Harvey by use of their

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15 Harvey Arch f path Anat 196 303, 1909

technic He, however, added to the strain on the vascular system in both cases Twelve rabbits were suspended by him for five minutes twice daily for 180 days, and six rabbits for five minutes twice daily for a whole year These animals accordingly received more than twice the "dose" which Klotz had given them He also compressed the aorta in twelve rabbits daily for five minutes for 180 days, and in six others for a full year The result was entirely negative, except for two animals that had been treated by suspension One of these animals died early in the experiment and the other showed a septic endometritis Steinbiss reached the obvious conclusion that the lesions found by Klotz and Harvey were caused by something other than the strain on the vessel wall

Aschoff tried to repeat Klotz' experiments but obtained entirely negative results Likewise Lubarsh, Starokadomsky, Tsobolow and Fahr failed to obtain vascular lesions by repeating Klotz' technic In the face of all these failures one is forced to doubt, with Steinbiss, whether experimental atherosclerosis has ever been caused by simple increased strain on the vessel wall

In summary, it may be said that, of all the methods tried, only the intravenous injection of bacteria and the feeding of animal food has consistently resulted in the production of experimental atherosclerosis Animal diets are abnormal for rabbits in at least two ways They contain an excess over herbivorous diets of both protein and cholesterol A number of workers have tried to prove that the vascular lesions occurring in rabbits fed animal diets were caused by the cholesterol It has, however, not yet been shown that a simple hypercholesterinemia can produce atherosclerosis The literature contains no record of a systematic investigation of the possible effect of the protein in the diet on the arteries of rabbits Our experiments were accordingly undertaken with the intention of establishing the relationships (if any existed) between diets characterized by their high content of protein and atherosclerosis

#### RECORD OF FEEDING EXPERIMENTS

*Composition of Diets*—Diets containing two different concentrations of protein were fed Lean beef muscle, mechanically freed of fat and then dried and powdered, was the chief source of protein Ordinary white bread flour, mixed in equal parts with bran, supplied carbohydrate and roughage The first diet was made by stirring together 1,000 gm powdered beef, 2,000 gm of the flour-bran mixture, 20 gm sodium chlorid, 50 gm baking powder and enough water to produce a stiff dough The latter was then spread thickly in oiled pans and baked in an oven at about 180 C until a dark brown crust had formed

The second diet contained 500 gm powdered beef, 2,000 gm of the flour-brian mixture, 20 gm sodium chlorid and 50 gm baking powder. It was prepared for feeding in the same way as the first diet.

An analysis for nitrogen by the Kjeldahl method of the powdered beef and of the two diets, gave the following values

100 gm dried powdered beef	= 13.0 gm nitrogen
100 gm first diet	= 5.8 gm nitrogen
100 gm second diet	= 4.3 gm nitrogen

Multiplying these nitrogen figures by 6.25 gives the following protein content

Dried powdered beef	= 81.2 per cent protein
First diet	= 36.2 per cent protein
Second diet	= 26.8 per cent protein

In addition to this food, the rabbits were each allowed about 100 gm of greens once a week.

The animals were obtained from fanciers who had taken special pains to raise them in clean, light, well ventilated pens. During the feeding experiments they lived in pens which had previously been made scrupulously clean and which were kept clean thereafter. Some of the rabbits were housed together in small groups. Many others lived throughout the experiment in individual cages. These cages were located in an unheated shed which protected the animals from wind and rain but which afforded them ample sunshine and ventilation. The date of birth of many of the rabbits was known and we were thus able to determine whether age played a part in the causation of the vascular lesions.

*Statistical Outcome*—Twenty-four animals lived for four weeks or more on the diet containing 36 per cent of protein. They may conveniently be divided into three groups determined by the duration of the experiment. In the first group are ten animals that lived from four to eight weeks on the diet. Two of these rabbits showed very early intimal disease. Six rabbits lived on the diet from ten to sixteen weeks and four of them showed early intimal disease. The remaining eight rabbits ate the high protein mixture from eighteen to thirty-six weeks and all of them presented marked and extensive atherosclerosis.

Fifty-one animals were fed the diet containing 27 per cent protein. These rabbits fall naturally into two groups—forty that lived less than twenty-six weeks, and eleven that lived from twenty-six to fifty-nine weeks. None of the forty rabbits that lived for less than six months on the diet containing 27 per cent protein showed atherosclerosis of the aorta, whereas eight of the eleven animals that ate this diet for more than six months presented aortic lesions which were grossly and histologically typical of true atherosclerosis. The vascular lesions in

seven of these eight rabbits were advanced and extensive. The eighth rabbit had eaten the diet for just six months and its aorta showed an early but widely distributed process.

On the basis of these results it is evident, first, that the animals which ate a diet containing 36 per cent protein showed the atherosclerosis sooner than did the rabbits that received only 27 per cent protein, and, second, that the occurrence and extent of the atherosclerosis was roughly proportional to the duration of the feeding.

*Description of Lesion*—The lesion as seen by the unaided eye is made up of discrete and confluent, raised, opaque white streaks and plaques. The process is always most marked in the upper thoracic aorta and in very early cases may be limited to a few closely set tiny plaques restricted to the arch. As the process becomes older and more marked, the individual lesions are larger and extend further down the aorta. In advanced examples, one of which is shown in Figure 1, the plaques and streaks may be thickly distributed along the whole aorta.

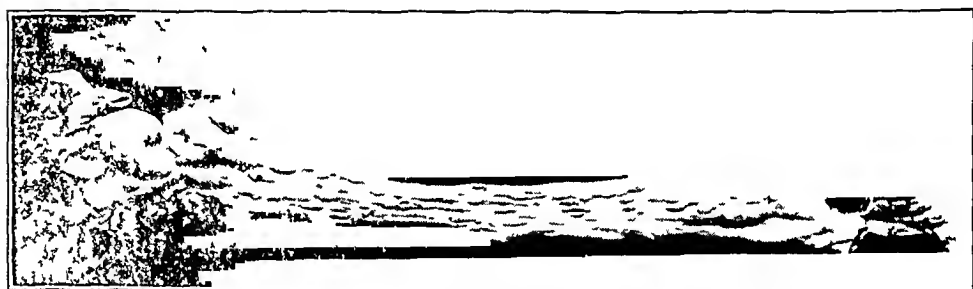


Fig 1 (Rabbit A-109)—Aorta of a rabbit fed a diet containing 27 per cent protein for nine months. The photograph shows many large irregular plaques and streaks. The normal intima of the arch is entirely replaced by a broad confluent plaque.

and may also extend a few centimeters into the great vessels given off by the aorta. In the upper aorta the fusion of the plaques often results in the entire disappearance of normal intima. Not infrequently the lesion involves the aortic valves causing them to become thick and stiff. In a few instances the mitral valve was similarly involved.

The lesion when examined with the microscope is seen to be a primary disease of the intima. It begins with a necrosis or fatty degeneration of the endothelial cells (Figs 3 and 4). The initial injury is very quickly followed by great thickening of the intima due to the presence in it of large cells loaded with fat and imbedded in a hyperplastic elastic tissue (Fig 5). At a somewhat later stage, when repair is being attempted the picture has added to it a broad band of fibrous elastic tissue on the lumen side of the vessel (Fig 6). Below this is the area of necrosis and fatty degeneration which by now has invaded

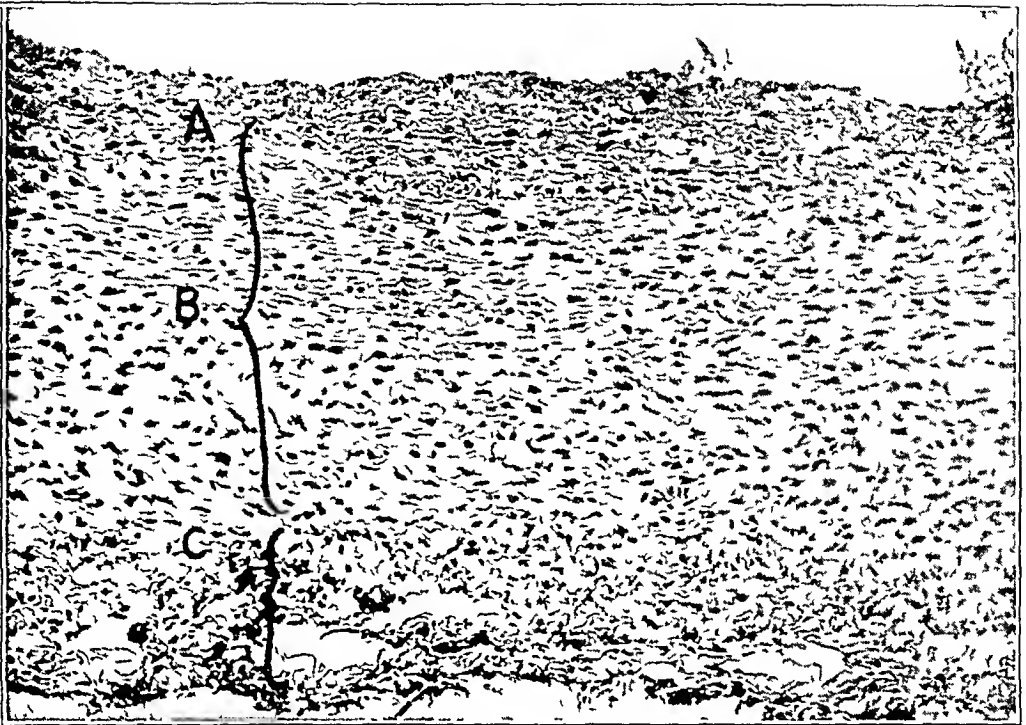


Fig 2—Normal aorta, hematoxylin and eosin *A*, narrow intima, *B*, broad muscular media, *C*, adventitia

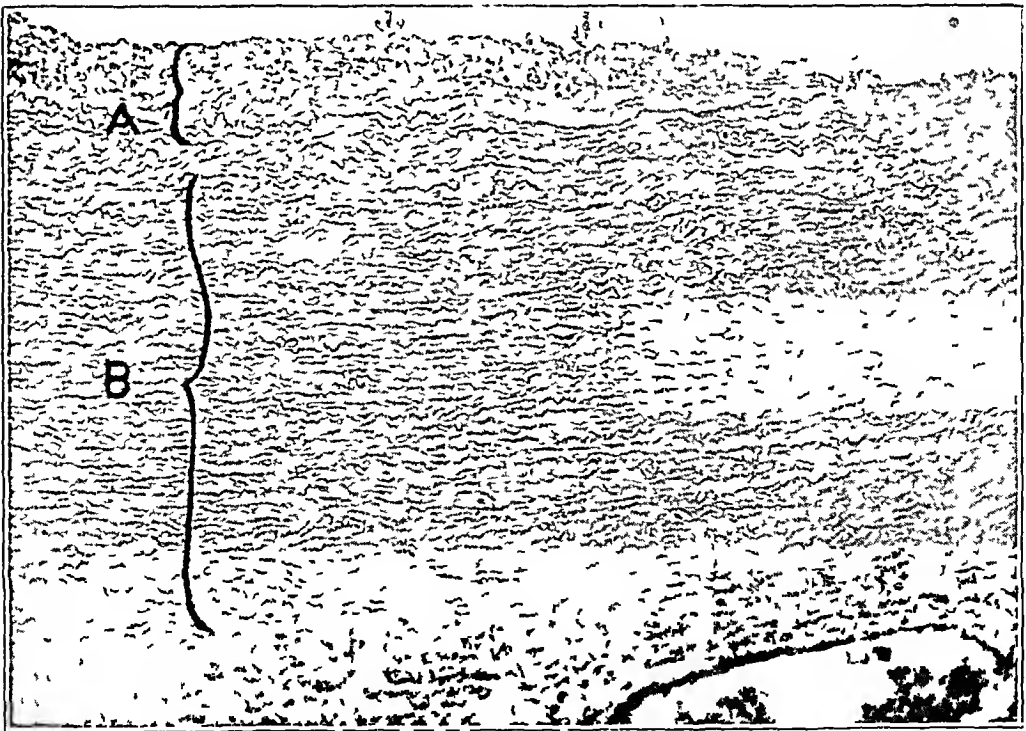


Fig 3 (Rabbit A-141)—Aorta of a rabbit fed a diet containing 36 per cent protein for eight weeks. Hematoxylin and eosin *A*, intima showing the early stages of atherosclerosis, *B*, media

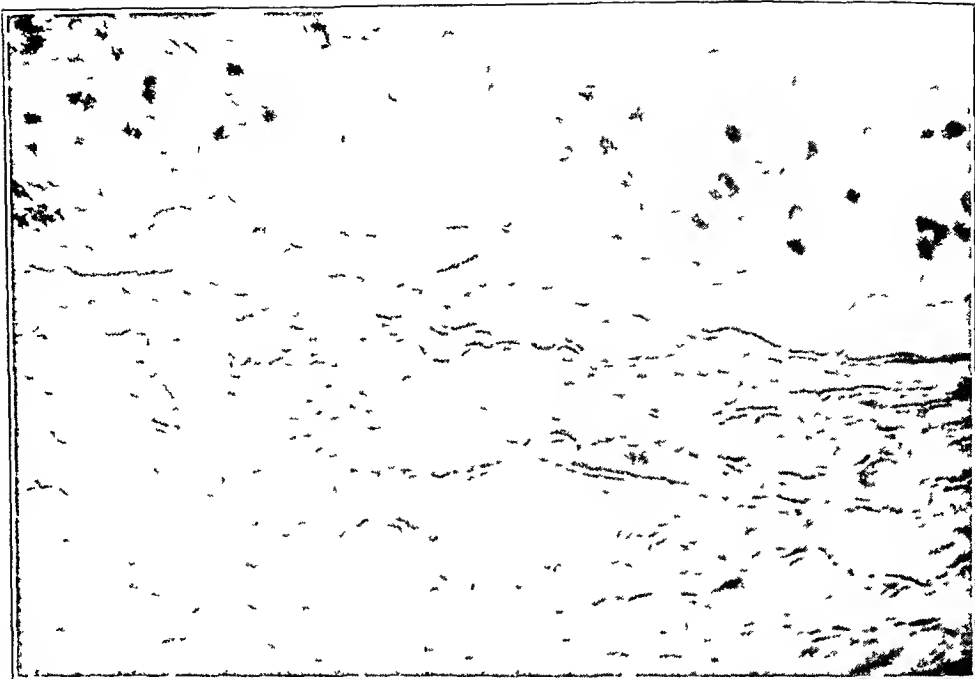


Fig 4—A high power view of the portion of the intima in Figure 3 indicated by the arrows. The intima cells show swelling, hyaline degeneration and vacuolization. Their nuclei are pyknotic. Fat stains demonstrated that many of the vacuoles were filled with fat.

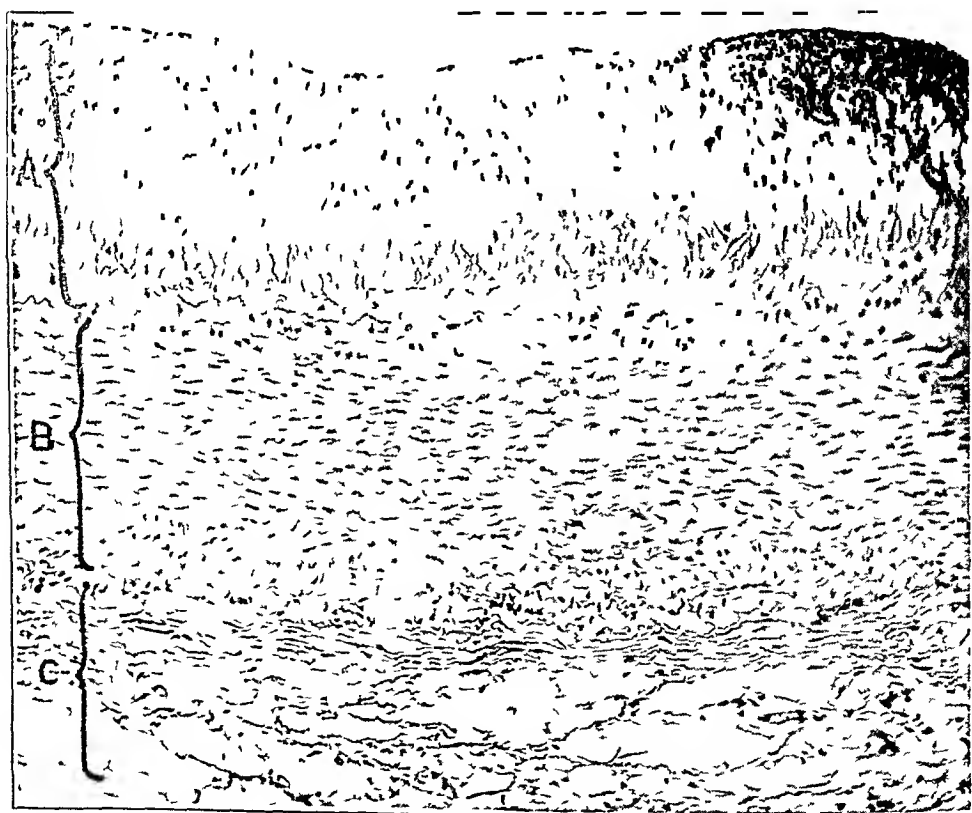


Fig 5 (Rabbit A-27)—Aorta, hematoxylin and eosin. Atherosclerosis moderately advanced. The rabbit was fed a diet containing 27 per cent protein for nine months. *A*, the great thickening of the intima brought about by the large vacuolated cells and the hyperplastic elastic tissue, *B*, normal media, *C*, adventitia.

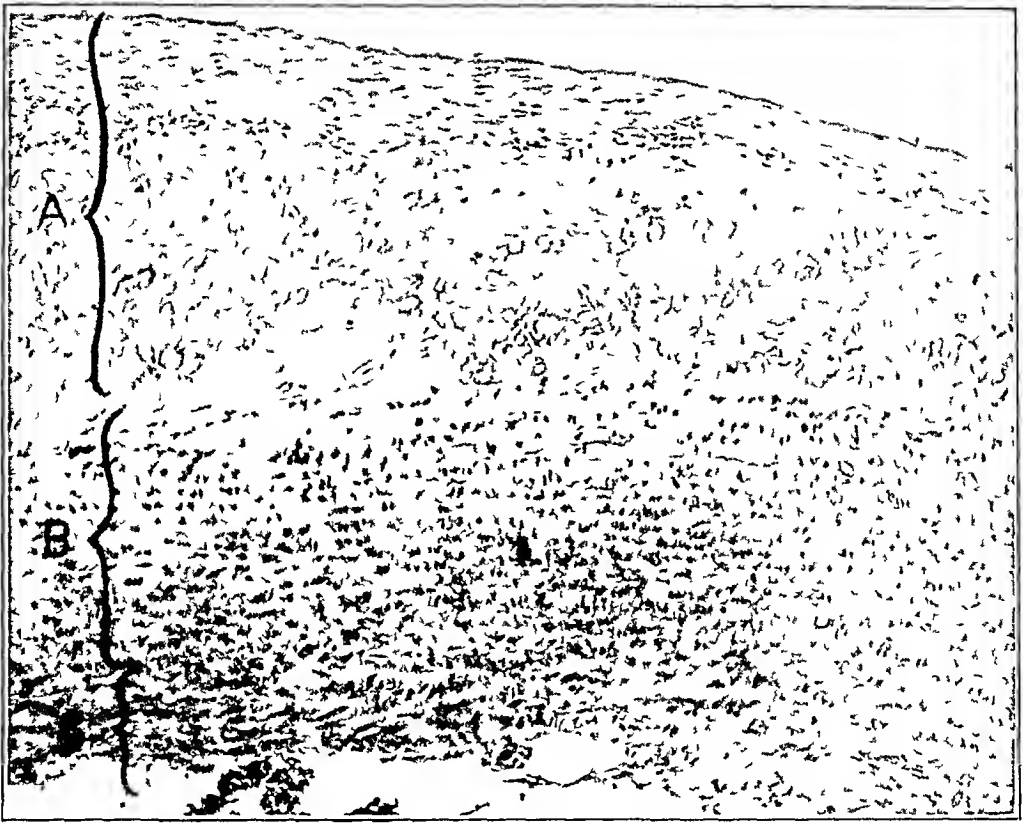


Fig 6 (Rabbit A-108) —Aorta , hematoxylin and eosin Atherosclerosis is far advanced The rabbit was fed a diet containing 27 per cent protein for eleven months A, intima showing a band of dense fibrous tissue on the lumen side of the vessel and degenerated fat containing cells below, B, the degeneration has progressed far into the media, C, adventitia



Fig 7 (Rabbit A-109) —Abdominal aorta of a rabbit fed a diet containing 27 per cent protein for nine months Hematoxylin and eosin The microphotograph shows a large irregular mass of calcium deposit involving most of the intima in this area and dipping down into the media



the media to a variable extent. At this stage in the process, amorphous masses of calcium may be found scattered irregularly through the degenerated portion of the lesion (Fig 7). When portions of the aorta fixed in formaldehyd are examined by means of frozen sections and stains for fat, a convincing demonstration of the enormous amount of lipid material present in the intima is obtained (Fig 8). The hyperplasia and fraying of the intimal elastic tissue so characteristic of this lesion is well shown in Figure 9 which is a microphotograph colored by an artist from the original.

The experimental production of atherosclerosis of the coronary arteries is of special interest because it offers another method for use

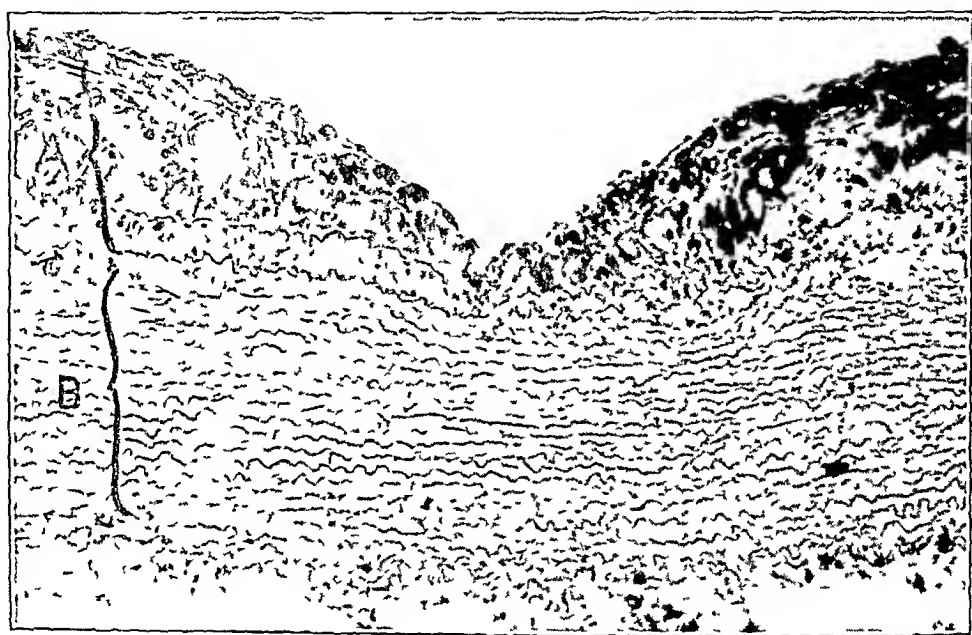


Fig 8 (Rabbit A-27)—Aorta, frozen section, sharlach R. *A* the black points and the irregular dark masses represent the lipid substances present in the intima, *B*, media

in the study of the etiology of myocarditis. The demonstration of an atherosclerotic process involving a small branch of the left coronary artery is presented in Figure 10.

#### CONTROLS

It has already been pointed out that the occurrence and extent of the atherosclerosis were roughly determined by the amount of protein in the diet and by the duration of the feeding. Such facts strongly suggest that the vascular lesions were produced by the high protein diets, but before being certain that such is the case it is necessary to investigate several possible sources of error.

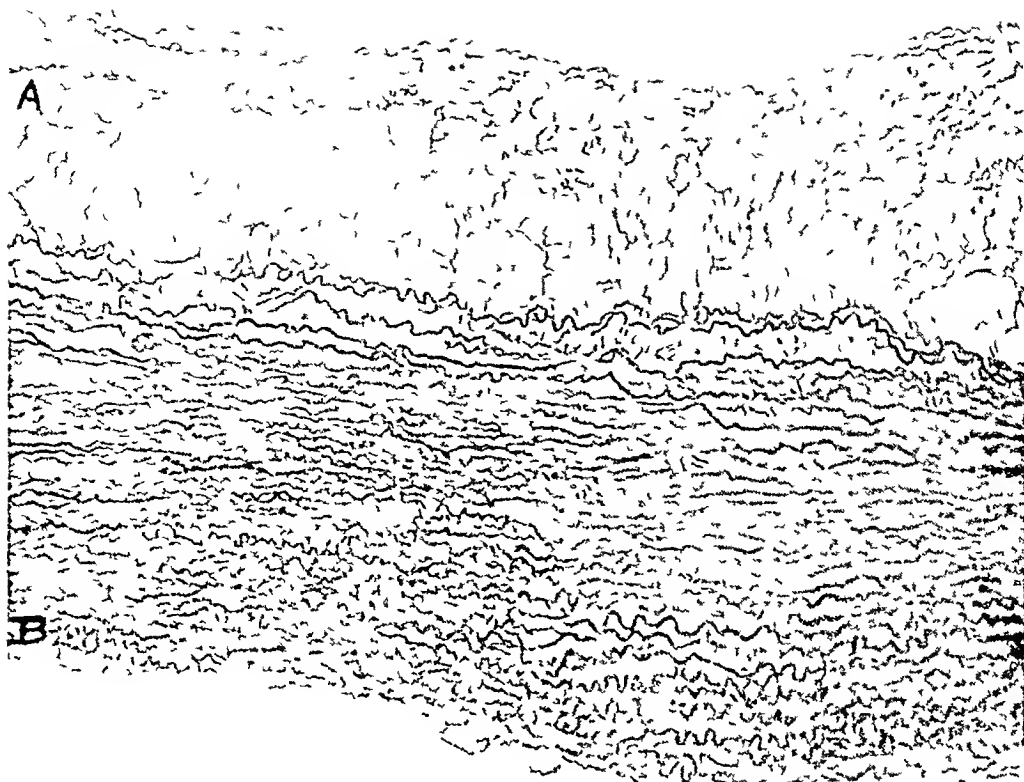


Fig 9 (Rabbit A-88) —Aorta, Weigert's elastic tissue stain *A*, the thickened intima showing the hyperplasia and fraying of the elastic tissue, *B*, media

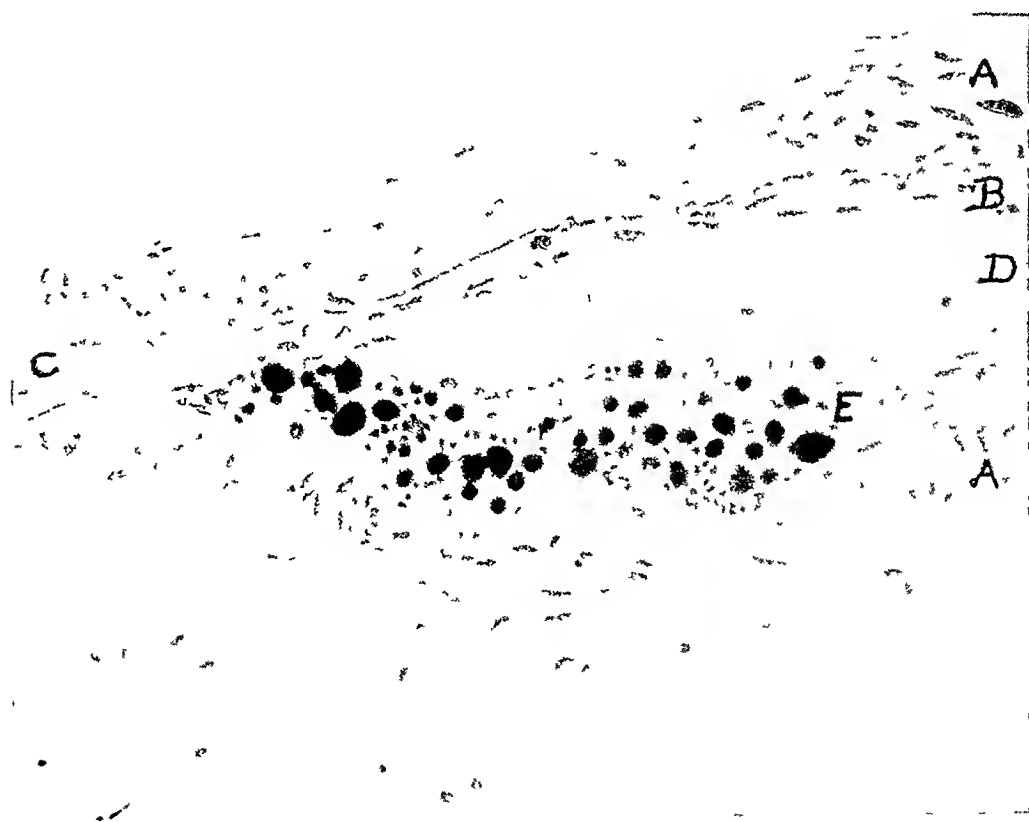


Fig 10—Myocardium showing a small artery, fat stain *A*, the media, *B*, the somewhat thickened intima. The area marked *EE* shows extensive fatty degeneration of the intima and involvement of the underlying media by the same process, *C*, indicates the lumen of the vessel, and *D*, a mass of blood cells lying in the lumen



*Spontaneous Atherosclerosis*—Until it is known how often primary intimal disease will be found in control rabbits, it is, at the very least, hazardous to attribute the atherosclerosis of the experimental animals to the diets. A number of investigators have obtained information in regard to this question.

Steinbiss<sup>8</sup> has examined the aortas of more than 500 rabbits. The group contained not only the laboratory animals but in addition many rabbits shot by hunters. With the exception of two questionable cases, he found no spontaneous atherosclerosis.

Loeb<sup>16</sup> examined 483 normal rabbits carefully without finding any arterial changes.

E. C. Rosenow<sup>17</sup> has noted the condition of the first portion of the aorta in 1,548 rabbits. There were atheromatous patches in only three. An additional 300 rabbits has recently been subjected to necropsy by him. Atherosclerosis of the beginning of the aorta was not found in a single instance.

Miles,<sup>18</sup> on the other hand, found aortic lesions in seventeen of forty-nine (34.6 per cent) supposedly normal rabbits. She adds that rabbits obtained from a dealer raising them for the market in large numbers and in close quarters showed a higher percentage of lesions than those obtained from other sources. The disease as described by her involved the media primarily and chiefly, and was identical with the epinephrin effects. Such necroses of the media have been frequently noted by several other investigators. They should not be confused with atherosclerosis and give us no information in regard to the spontaneous occurrence of disease of the intima in rabbits.

Levin and Larkin (quoted by Steinbiss<sup>8</sup>) report finding spontaneous atherosclerosis in 13 per cent of rabbits. The material consisted of animals that had been injected with blood serum and "nontoxic substances." Since the nature of the "nontoxic substances" is not mentioned, one may still question whether some of these substances were not after all toxic for the blood vessels. It may also be questioned whether the injection of blood serum may not result in the formation of substances injurious to blood vessels. In any case, there is no more ground for using such material as a control than there would be if it were presented as evidence that the substances injected by Levin and Larkin were injurious to the blood vessels.

We have carefully examined the aorta in 116 rabbits obtained from several sources. Twenty of these animals had been used in the laboratory course in pharmacology to demonstrate the action of drugs. The aortas of all of these rabbits were normal. Seventy-seven rabbits were

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16 Loeb. *Deutsch Med Wchnschr* **39** 1819, 1913.

17 Rosenow. Personal communication.

18 Miles. *J A M A* **49** 1173 (Oct 5) 1907.

obtained from the hospital laboratory. Many of them had been bled to death, the blood being used to make culture mediums. A few of them had received injections of bacteria some weeks before they were killed. A few others were found dead in the stock cages. Of these seventy-seven rabbits, four that had been used for bleeding, showed abnormalities of the upper aorta. The remaining seventy-three rabbits presented normal aortas.

*Effect of Laboratory Environment*—Nineteen of the 116 control rabbits formed a special group. These animals were set aside in the ordinary laboratory pen for the purpose of answering two questions: (1) whether the conditions prevailing in our laboratory were, when long continued, in themselves a cause of atherosclerosis, and (2) whether age was a factor in the production of atherosclerosis. These rabbits were given the same food as the stock animals. No special precautions were taken to protect them from infection. They were, on the contrary, exposed to the infections brought in by newcomers in adjoining cages. When one of these control rabbits became infected, it was still left in the pen with the other controls. Three of these nineteen rabbits had been injected with bacteria before being placed in the control pen. One had received six intravenous injections of diphtheria bacilli, the second one received repeated injections of dead typhoid bacilli and the third one (A 83) received six intravenous injections of *Streptococcus hemolyticus*. This animal lived in the control pen for a year following the injections. He underwent a progressive emaciation with a fall in weight from 2,250 gm to 1,380 gm during the year. For many weeks preceding his death he suffered from very severe "mange" accompanied by ulceration of the skin. His aorta was normal, except for the presence in the arch of several pale yellow wartlike papules just visible to the naked eye.

The rabbit that received the injections of diphtheria bacilli lived in the control pen nine months. He also showed a progressive emaciation and severe mange. His weight fell to 1,110 gm. His aorta was normal.

The rabbit injected with dead typhoid bacilli died after being in the control pen for five months. At the necropsy a caseous pneumonia of the upper and middle lobes of the right lung and an extensive fibrous pericarditis was found. His aorta was normal.

Sixteen of these nineteen rabbits were placed in the control pen when they were about 6 months old. Three of them died within six weeks, three lived from two to four months, three lived six months, three lived more than six months but less than one year, four lived more than one year, fifteen died directly or indirectly of infection. Acute pneumonia killed a few of them. Protracted "snuffles," accompanied by marked wasting and often complicated by bronchopneumonia, caused the death of many of the rabbits. None of them showed lesions of the aorta.

We wish to emphasize the point that these fifteen rabbits died of the infections to which all the animals in the laboratory were exposed. Some of them were killed quickly but a majority of them bore their infection a number of months. Nevertheless, no disease of the aorta was seen in any of them. We have accordingly reached the conclusion that the infections which were prevalent in our laboratory during the period of our experiments were not a cause of atherosclerosis, even though some of these infections were chronic in type and remained active for months. This statement may occasion some surprise since there are good reasons for believing that pathogenic bacteria cause atherosclerosis in rabbits, but in spite of this it is a fact that the types of spontaneous infection from which these fifteen rabbits suffered, did not cause vascular disease in them.

The special group of nineteen rabbits used to discover whether conditions in the laboratory were such as to be a cause of atherosclerosis contained only one animal whose aorta was not normal. This was rabbit A 83, already mentioned. The microscopic examination of the small wartlike papules seen on the surface of the aorta, showed that they consisted of fibrous connective tissue. No hyperplasia of the elastic lamina was visible and no fat was present in the lesion. These are the features of a healed process. Since this animal had received intravenous injections of the hemolytic streptococcus a year before his death, the streptococcus may have caused the aortic lesion. At all events, this is an adequate explanation for the lesion, which accordingly need not be attributed to any conditions arising after this rabbit was placed in the special control group.

Since eighteen of these nineteen rabbits showed no vascular disease, even though most of them had lived in the laboratory for many months in such a way as to receive no special care or protection, it is evident that the laboratory conditions were not such as to cause atherosclerosis.

*Calcification of Media*—There were four rabbits, in addition to A 83, among the control group of 116 (3.4 per cent) whose aortas were abnormal. The vascular lesions found in these animals were, without exception, very small in extent. They consisted of one or several tiny papules rising above the surface of the intima in the ascending limb or arch of the aorta. They were so small that they were often seen by the unaided eye only when especially sought for.

Among the treated animals, four of those that were fed the diet containing 27 per cent protein, and two of those that received the food containing 36 per cent protein—a total of six out of eighty-two (7 per cent)—showed vascular lesions of this same type.

These abnormalities of the aorta were easily distinguished from the primary intimal disease which occurred in the animals fed the high protein diets. In the former, the lesions were always restricted to the

uppermost part of the aorta and bore no special relation to the openings of the small vessels. The individual lesions were always small, at most 2 or 3 mm in diameter, whereas in the latter the lesions were much larger, took the form of large irregular plaques and broad bands, were often widely distributed along the thoracic aorta and showed a striking tendency to be most marked around the openings of the small vessels.

On microscopic examination, it was found that these lesions were, without exception, situated in the media. Bands of muscle cells were necrotic and very often calcified. The process appeared to have a

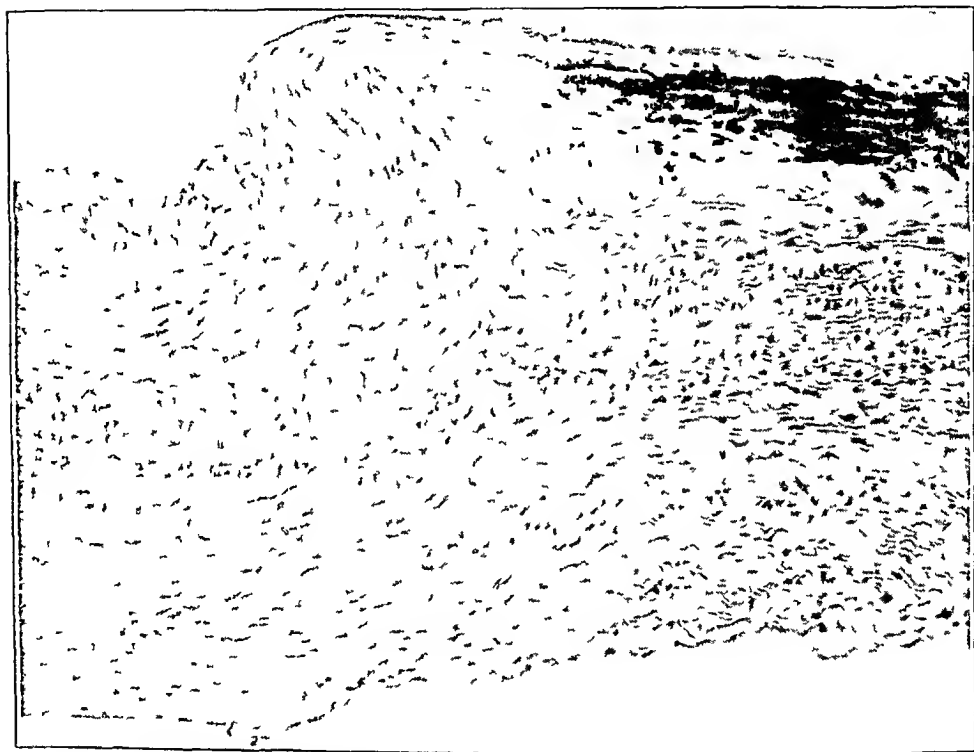


Fig 11 (Rabbit A-2)—Control, aorta. The upper media shows calcified muscle cells. The overlying intima is normal.

predilection for the upper media but did not extend into the intima. A typical example of this condition is represented by Figure 11. The absence of fat in this medial lesion, and its abundance in the atherosclerosis of the meat-fed animals, was alone sufficient to make a sharp differentiation between these two processes.

On the basis of the experience of other investigators, and as a result of the careful study of our own 116 control rabbits, we have concluded that (1) in any large series an occasional supposedly normal rabbit may be expected to show small restricted vascular lesions, (2) these lesions can by means of the microscope and special stains, easily be

distinguished from the extensive fatty intimal disease seen in rabbits that have eaten the experimental diets for some weeks, (3) long exposure to the conditions existing in our laboratory does not cause atherosclerosis

*Age*—In the case of man, age is an important predisposing factor in the causation of atherosclerosis. It might be argued that this also held true for the rabbit and that our rabbits were atherosclerotic because they were old. An answer to this question may be obtained by comparing the ages at death of rabbits of known age in the control group that had lived in the laboratory for more than six months with similar rabbits that had eaten a high protein diet for six months or more. Table 1 shows that the control rabbits whose aortas were normal were as a group older than the atherosclerotic rabbits, and that the three rabbits which had not developed atherosclerosis, even though they had eaten the high protein mixture for more than six months, were, on the

TABLE 1—LACK OF RELATION BETWEEN AGE AND ATHEROSCLEROSIS

Ate Diet Containing 27 per Cent Protein for Six Months or More				Controls That Lived in the Laboratory More Than Six Months	
Number	Normal Aorta, Age at Death	Number	Atherosclerosis, Age at Death	Number	Normal Aorta, Age at Death
A-61	62 weeks	A-67	50 weeks	A- 1	41 weeks
A-78	68 weeks	A-27	58 weeks	A- 5	42 weeks
A-60	87 weeks	A-26	61 weeks	A-74	46 weeks
		A-61	62 weeks	A-81	58 weeks
		A-77	70 weeks	A-12	61 weeks
				A-37	66 weeks
				A-52	73 weeks
				A-71	84 weeks
				A-84	92 weeks
Averages	72 weeks		60 weeks		68 weeks

average, older than the animals which showed the aortic disease. It is evident that the atherosclerosis found in the meat eating rabbits was not caused by old age.

*Infection*—It has already been shown that the infections which were prevalent in the laboratory did not produce atherosclerosis in rabbits to which normal food was fed. It might, however, be suspected that the high protein diet could produce metabolic disturbances which would make it possible for such laboratory infections to injure the intima; or that such a diet could break down the resistance (possessed by normal rabbits) to those bacteria in themselves capable of causing atherosclerosis. One would expect to be able to detect the presence of such hypothetical metabolic disturbances by their impress on the general condition of the animals. An opinion regarding an animal's general condition may be obtained by observing its coat and its conjunctivae, the rate at which it grows, its maximum weight. Our high protein rabbits presented the smooth coat and bright eyes of health and in this



respect appeared more nearly normal than the controls Table 2 presents the maximum weights attained by rabbits fed a diet containing 27 per cent protein and by controls, all of which had lived in the laboratory at least six months It will be seen that the high protein rabbits reached a much greater adult weight than the controls Three of the rabbits eating the high protein mixture were killed at a time when they presented the appearance of perfect health Two of them gave the most

TABLE 2—MAXIMUM WEIGHT AND MODE OF DEATH OF RABBITS LIVING IN THE LABORATORY SIX MONTHS OR MORE

Fed Diet Containing 27 per Cent Protein						Normal Diet		
Became Atherosclerotic			Aorta Remained Normal			Aorta Was Normal		
Num ber	Maxi mum Weight, Gm	Mode of Death	Num ber	Maxi mum Weight, Gm	Mode of Death	Num ber	Maxi mum Weight, Gm	Mode of Death
A-77	2,770	Found dead	A-78	2,750	Lethargy, killed	A-1	1,670	Found dead
A-27	2,600	Found dead	A-118	2,670	Severe "mange", dy- ing, killed	A-5	1,850	Diarrhea, found dead
A-67	2,040	Lethargy, killed	A-61	2,600	Found dead	A-12	1,550	Found dead, bilateral purulent pneumonia
A-109	2,850	Dying, killed	A-60	2,800	Appearance of health, killed	A-74	1,450	Found dead
A-88	2,040	Lethargy, killed				A-68	1,290	Severe snuf- fles found dead
A-26	2,640	Found dead				A-84	1,380	Dying, killed
A-100	3,270	Appearance of robust health, killed				A-52	2,750	Dying, killed, broncho- pneumonia
A-108	3,700	Appearance of robust health, killed				A-71	3,000	Mange, found dead
						A-37	1,450	Found dead
						A-81	1,690	Found dead
Average	2,770			2,700			1,812	

extensive examples of atherosclerosis in the series They were also the heaviest rabbits in the series

We were thus unable to obtain any support for the idea that nutritional disturbances attendant on the high protein diet had resulted in the invasion or growth of bacteria But our evidence is of a negative sort It is impossible to prove absolutely that bacteria had no part in the causation of this lesion It is, however, a fact that the bacteria which infected the control rabbits and eventually killed all but one of them were incapable of producing atherosclerosis in rabbits which received normal food Hence, it must be true that the high protein

diet was the determining factor in the occurrence of the atherosclerosis. If bacteria or their toxins had anything to do with the etiology of this disease, their contribution must have been of a secondary and relatively unimportant nature.

*Cholesterol*—The possible place of cholesterol in the etiology of experimental atherosclerosis has already been discussed. It will be recalled that several investigators held the view that the atherosclerosis which occurred in rabbits fed various kinds of abnormal diets was in every instance caused by the cholesterol of the diet. Wesselkin,<sup>19</sup> who fed one egg yolk daily (cholesterol content, 64 mg) for six months, Starokadomski<sup>20</sup> who fed two egg yolks daily for nine weeks, and Saltykow<sup>21</sup> who fed 400 c.c. milk (cholesterol content, 48 mg) for more than one year, were each convinced that the cholesterol in the food was responsible for the intimal disease. These were the smallest doses used by students of this question who obtained positive results. It is of interest to compare the cholesterol content of our diet<sup>22</sup> with these minima. One hundred grams of dried powdered beef yielded 190 mg cholesterol. Since the average twenty-four hour urinary nitrogen of rabbits on the diet containing 27 per cent protein was 2 gm, they must have obtained about 12 gm protein daily from the diet. Most of this protein was derived from the beef and it has higher cholesterol values than the other ingredients of the diet. If all of the protein had come from the beef (protein 82 per cent), each rabbit would have absorbed about 15 gm of dried beef daily and this would have made possible a maximum of 28 mg cholesterol daily. Hence the amount of cholesterol received by our rabbits was 22 per cent of the amount fed by Starokadomski, 44 per cent of that used by Wesselkin, and 58 per cent of that eaten by Saltykow's rabbits. The amount of cholesterol ingested by our rabbits was accordingly much less than the smallest amounts said to have caused atherosclerosis.

Saltykow fed about twice the amount of cholesterol contained in our diet. His series consisted of six rabbits that received daily 400 c.c. milk each. The animals lived from one to two years and two and one-half months. Three rabbits showed extensive atherosclerosis and one presented no intimal disease. On the other hand, eight of our eleven rabbits which ate a high protein diet with its daily dose of 28 mg cholesterol developed widespread atherosclerosis in from six months to one year. Even if it were admitted that the 48 mg cholesterol contained in Saltykow's diet had caused advanced atherosclerosis in 50 per cent of the animals that ate this diet one year or more, this would not prove, or even strongly suggest, that the extensive intimal disease found

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19 Wesselkin. *Rusky Vrach*, p 1651, 1912.

20 Starokadomski. *Frankfurt Ztschr f Path* 3 912, 1909.

21 Saltykow. *Arch f path Anat* 213 8, 1913.

22 We are grateful to Dr H. G. Waller for the cholesterol determinations.

in 73 per cent of our rabbits that had received about half this amount of cholesterol daily for about half the length of time was caused by the cholesterol

In answer to the criticism that the vascular disease found in the milk-fed rabbits was not caused by cholesterol, Saltykow pointed out that Wesselkin had fed a total of 11 52 gm cholesterol per rabbit in six months, Starokadomski a total of 8 064 gm in nine weeks, whereas his own total was from three to five times greater—about 37 gm—because of the duration of his experiments

If we apply this same type of calculation to our experiments, it is found that the average total dose of cholesterol was 7 56 gm for the eleven rabbits that ate the diet containing 27 per cent protein from six months to one year, and 6 993 gm for a group of eight rabbits all of which developed marked atherosclerosis within six months on a diet containing 36 per cent protein. Hence, the total dose received by our rabbits was less than that used by Wesselkin or Starokadomski and much less than that fed by Saltykow

Since both the daily and the total dose of cholesterol received by our rabbits was so much less than that considered by other investigators necessary to cause atherosclerosis, it does not seem likely that the cholesterol in our diets played an important rôle in the etiology of the atherosclerosis which we are reporting

#### SUMMARY

The term atherosclerosis should be applied only to primary disease of the intima characterized by fatty degeneration and hyperplasia of the elastic tissue. Investigators have obtained this lesion experimentally by injecting bacteria and by feeding abnormal diets. Many students of experimental alimentary atherosclerosis believe that the cholesterol contained in the abnormal diets is the sole cause of the intimal disease. The reasons why we do not concur in this view have been discussed. Many of the experimental diets used by earlier workers were abnormally high in protein, but this factor received no special study. Our experiments have shown that the prolonged ingestion of excessive amounts of protein by rabbits will result in extensive atherosclerosis of the aorta and several other arteries. Study of sources of error has demonstrated that the atherosclerosis found in the rabbits that ate the high protein diets was not spontaneous, was not the effect of laboratory environment, age or infection, could easily be distinguished from the spontaneous calcification of the media, and was not caused by the small amount of cholesterol in the diet.

# THE PRESENCE OF AUER BODIES IN LEUKEMIC TISSUES

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Since the discovery by Auer,<sup>1</sup> in 1906, of certain rodlike bodies in the red blood cells in a case of acute leukemia, several additional articles have appeared, dealing with the character of these bodies and the type of cell in which they are found. Inasmuch as the literature on the subject is still meager, the report of an additional case may be of some value. The case is of special interest since it is the first, as far as can be ascertained, in which the Auer bodies have been demonstrated in microscopic sections of the various organs.

A résumé of the literature reveals little that was not described in Auer's report. Auer noted that rod-shaped bodies were visible as refractive objects in the cytoplasm of from 6 to 10 per cent of the "large lymphocytes," in preparations of fresh blood, that they were stained clearly (red) by Wright's and Leishman's stains, faintly by Ehrlich's triacid mixture, but not by Ehrlich's haematoxylin and eosin, methylene blue and eosin, Loeffler's methylene blue, sudan III or Lugol's solution. The rods were found free in the blood only in the vicinity of disintegrated cells, and once were seen in the cytoplasm of a normoblast.

Similar findings were later reported by other authors. Pappenheim,<sup>2</sup> Pappenheim and Hirschfeld,<sup>3</sup> Ottenberg,<sup>4</sup> Isaac and Cobliner,<sup>5</sup> and Naegeli<sup>6</sup> found Auer bodies in "large lymphocytes." Ottenberg inoculated monkeys with fresh blood and with splenic pulp, but neither transmitted the Auer bodies nor produced leukemia. Roth<sup>7</sup> reported Auer bodies in a case of subacute miliary tuberculosis with certain symptoms that may be interpreted as leukemic. The blood in his case,

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\* From the Pathological Laboratories of Bellevue and Allied Hospitals.

1 Auer, J. Some Hitherto Undescribed Structures Found in the Large Lymphocytes of a Case of Acute Leukemia, *Am J M Sc* **131** 1002, 1906.

2 Pappenheim, A. Ueber eigenartige Zelleinschlüsse bei Leukämie, *Berl klin Wchnschr* **45** 60, 1908.

3 Pappenheim and Hirschfeld. Ueber akute myeloide und lymphadenoide makrolymphozytare Leukämie an der Hand von zwei verschiedenen Fällen, *Folia haematol* **5** 347, 1908.

4 Ottenberg, R. Observations on Acute Leukemia, with Special Reference to Auer's Bodies, *Am J M Sc* **138** 562, 1909.

5 Isaac and Cobliner. Ueber mikrolymphozytare Typen akuter myeloischer Leukämien, *Folia haematol* **10** 459, 1910.

6 Naegeli, O. Blutkrankheiten und Blutdiagnostik, Ed 2, Leipzig, Veit u Comp, 1912, p 482.

7 Roth, O. Ueber einen bemerkenswerten Blutbefund bei einem Fall von subakuter Miliartuberkulose, *Ztschr f klin Med* **78** 75, 1913.

as in the one reported herewith, contained a high percentage of "myeloblasts" in which the Auer bodies were found Chosrojeff<sup>8</sup> also found Auer bodies in "myeloblasts," and thinks it possible that in earlier cases cells reported as large lymphocytes may have been myeloblasts In this case Auer bodies were found in smears of the bone marrow, spleen and lymph nodes, but no mention is made of their presence in tissue sections Rosenthal<sup>9</sup> found Auer bodies in "myelogones" and noted that they gave a positive oxidase reaction Thro<sup>10</sup> reported red staining rod-shaped granules in "myeloblasts" but gives no further description of their morphology and staining reactions It appears from his illustrations that they may have been Auer bodies Nakajima,<sup>11</sup> Yoshida,<sup>12</sup> and Ishikawa<sup>13</sup> also reported finding Auer bodies in myelogenous leukemia Ishikawa tried numerous stains on blood smears, and found the bodies well stained by the Romanowsky methods, poorly stained by Ehrlich's triacid or eosin stain, positively stained in the indophenolblue synthesis, and stained blue by pyronin They were vitally stainable without metachromatism by gentian violet and safranin They did not stain with sudan III, Loeffler's methylene blue, Gram stain, Gabbett's stain for tubercle bacilli, or the Levaditi silver method In tissues fixed in liquor formaldehyd, cut by the paraffin, celloidin and frozen section methods and stained by hematoxylin and eosin, Giemsa and oxidase stains, no Auer bodies were seen In Ishikawa's cases, aerobic and anaerobic cultures of blood were negative, and inoculation of mice, rabbits, guinea-pigs and apes gave negative results Here, too, the leukemia was of the myeloblastic type

#### REPORT OF CASE

*History*—The patient, an Italian woman, aged 23, was admitted to the wards of the Fourth Medical Division, Bellevue Hospital, with the following history

Two weeks before admission, she experienced pain behind the sternum, sore throat nonproductive cough, dyspnea, headache and fever During the last four days these symptoms became worse, the gums became swollen and tender, and a swelling appeared on the right side of the face and neck

*Physical Examination*—On examination, the woman appeared to be acutely ill The mucous membranes were pale, and the skin was lemon-yellow There was a tender swelling over the right side of the jaw and neck, without redness or fluctuation The cervical lymph nodes were enlarged and tender The throat was congested, the gums were swollen and tender, especially on the right side, and there was a cavity in one molar tooth There were hemorrhages in both

8 Chosrojeff, G P Myelosis Aleukaemica Acuta Micromyeloblastica, *Folia haematol* 20 33, 1915

9 Rosenthal, N Studies on the Oxidase Reaction of the Cells in Normal and Leukemic Blood, *Arch Int Med* 20 184 (Aug) 1917

10 Thro, W C Some Unusual Blood Cells in Diseases of Bone Marrow *Origin J M Research* 38 385, 1918

11 Nakajima Quoted by Ishikawa<sup>13</sup>

12 Yoshida Quoted by Ishikawa<sup>13</sup>

13 Ishikawa T Ueber den Auerkörper bei einem Falle von akuter Myeloblastenleukämie, *Mitt a d Med Fakult d k Univ zu Tokyo* 22 321, 1919

eye grounds The spleen was not palpable and the lymph nodes, with the exception of the cervical nodes, were not enlarged The rest of the history and physical examination was unimportant

*Laboratory Findings*—The urine was negative No Bence-Jones body was found on two examinations The single blood culture made was sterile Blood count On admission, the red cells numbered 1,900,000, the hemoglobin, 30 per cent The red cells rose to 4,000,000 and the hemoglobin to 65 per cent after transfusion, but rapidly declined again The white cells on several examinations were nearly constant, numbering between 6,000 and 8,000 Differential counts are given in the accompanying table

TABLE OF DIFFERENTIAL COUNTS \*

Date	Neutrophils	Lymphocytes	Mono- cytes	Eosino- phils	Neutro- phil Myelo- cytes	Eosino- phil Myelo- cytes	Myelo- blasts†	Per Cent Myelo- blasts with Auer Bodies‡	Plasma Cells
2/16/22	26	28.6	0	0.4	5.2	0.2	63.0	32.0	0
2/17/22	52	31.3	1.1	0	1.0	0.2	60.0	30.7	1.2
2/24/22	39	8.6	0	0	7.2	0.8	79.5	36.8	0
3/3/22	24	18.3	3.7	0.4	7.8	0	66.6	28.1	0.8

\* The counts were made on smears stained with Wright's or Jenner Giemsa stains, and are based on counts of at least 500 cells

† These cells were atypical The term "myeloblast" is used to indicate a cell in an early stage of myeloid differentiation, before definite granules can be demonstrated with ordinary stains (vide infra)

‡ The highest percentage of myeloblasts containing Auer bodies previously reported was by Ishikawa,<sup>13</sup> from 17 to 19 per cent They are often found in much less than 1 per cent of the myeloblasts

*Subsequent Course*—About two weeks after admission, the spleen became palpable and remained just below the costal margin Five weeks after admission, a peritonsillar abscess developed and was opened The temperature oscillated between 99 and 102 F, except during a chill following transfusion, when it rose temporarily to 105.8 F, and during the last few days of life, when it remained nearly constant at 104 F The patient died at the end of her fifth week in the hospital

#### NECROPSY FINDINGS

*Macroscopic Examination*—The changes found at necropsy were not marked Except for an enlarged spleen and a few petechial hemorrhages in the larynx and ileum, the gross findings were not remarkable The spleen weighed 325 gm and presented, on section, numerous lymph follicles of normal size

*Microscopic Examination*—Microscopic examination of the organs showed the presence of myeloblasts in the blood vessels, but no leukemic nodules or infiltrations Tissues were fixed in Helly's fluid and in liquor formaldehyd, sectioned by the celloidin, paraffin and frozen section methods, and stained with hematoxylin and eosin, Dominici's stain, azure II and eosin, Giemsa, Wright's blood stain, Goodpasture's acid polychrome-methylene blue and eosin,<sup>14</sup> Gabbett's stain, Gram's stain, and Graham's<sup>15</sup> oxidase method

In all of these stains except the hematoxylin and eosin stain, Gabbett's stain and Gram's stain, Auer bodies were distinctly seen in some of the myeloblasts The various methods were not equally satisfactory for their demonstration,

14 Goodpasture, E W An Acid Polychrome-Methylene Blue Solution for Routine and Special Staining, J A M A 69 998 (Sept 22) 1917

15 Graham, G S The Oxidising Ferment of the Myelocyte Series of Cells and Its Demonstration by an Alphanaphthol-Pyronin Method, J M Research 35 231, 1916

however, as the bodies were more numerous, larger, and very much more distinct in the oxidase preparations (in which they reacted positively) than in any other (Fig 3) Goodpasture's, Giemsa and Wright's blood stains, following Helly's fixation, were also very satisfactory. In azure-eosin or Dominici preparations fewer Auer bodies were seen.

(a) The Bone Marrow. Sections from the vertebrae and ribs contained the normal marrow elements, but the myeloblasts were somewhat increased in number, some of them containing Auer bodies.

(b) The Spleen. The spleen was the most interesting of the organs. Its fundamental structure was preserved. The follicles were normal in size, and presented two distinct zones: a central portion composed of typical small and medium sized lymphocytes, and a peripheral portion the cells of which were larger, with paler nuclei and a pale lavender cytoplasm.

The splenic pulp was very cellular. In the blood sinusoids were numerous myeloblasts, some of which had apparently attached themselves to the vessel walls and wandered out by amoeboid movement. Numerous examples of myeloblasts half within and half outside of the blood vessels were visible, some of them containing Auer bodies.

In addition to the myeloblasts were small groups of typical plasma cells, with transitional stages between them and lymphocytes. There were also occasional eosinophilic myelocytes.

The endothelium of the sinusoids was intact, the cells of the smaller vessels bulging sharply into the lumen, as is normal.

The myeloblasts of the pulp were closely grouped around the follicles. There was no admixture of follicular and pulp elements, however, the zone of contact being sharply defined. This perifollicular accumulation of myeloblasts was best seen with the oxidase stain, the follicles themselves reacting negatively and the perifollicular zone positively.

The splenic pulp (and lymph node) also contained a number of globular bodies, varying in diameter from about 1 to 15 microns. The smaller ones occurred in plasma cells. The larger globules so distorted the cell that its nature could not be determined. As a rule, there were groups of globules, with considerable variation in size within the group. With Dominici's stain, the globules were purple, with Gram's method they retained the dye, in the oxidase preparations they reacted positively and appeared as homogeneous structures.

(c) Lymph Node. Sections of a lymph node showed that some of the follicles were relatively normal. In others there were large numbers of plasma cells, a few of them containing purplish globules. When the cells were filled with these globules, they closely resembled the "mulberry cells" of Weber<sup>16</sup>. They appeared to be the same as those seen in the splenic pulp.

The other organs presented no important changes, except for the presence of myeloblasts in the blood vessels, some with Auer bodies.

#### DISCUSSION

From the standpoint of diagnosis, an important feature of the blood picture is the high percentage of myeloblasts and all transitional stages to the myelocyte. This, with the normal total white count, places the case clinically in the class of "aleukemic myeloblastic leukemia" or "acute aleukemic myelosis."

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16 Weber and Blendinger. A Note on "Mulberry Cells" and Clusters of Eosinophil Spherules, Probably a Form of Russell's "Fuchsine Bodies" in the Wall of a Chronic Cerebral Abscess and in a Case of Multiple Myeloma, *J Path & Bacteriol* 11: 59, 1906.

Gorham<sup>17</sup> has critically reviewed the reported cases of acute myelogenous leukemia, and gives five essentials for diagnosis (1) An aleukemic or subleukemic stage (2) An acute downward course with death usually ensuing in one to four months (3) Characteristic blood picture of myeloblasts and myelocytes, with transition forms between the two (4) Typical gross and histologic findings in the liver, spleen, bone marrow and lymph nodes (5) Specific proof of myeloid elements by enzyme reactions

The present case easily satisfies four of these points. There is room for argument, however, in that grossly and microscopically the pathologic changes were not very marked. It must be remembered that histologic changes similar to those of leukemia, but less extensive, may occur in acute infections.

*The Myeloblasts*—Since Auer bodies have been described in "large lymphocytes," "myelogones," and "myeloblasts," it is important in the

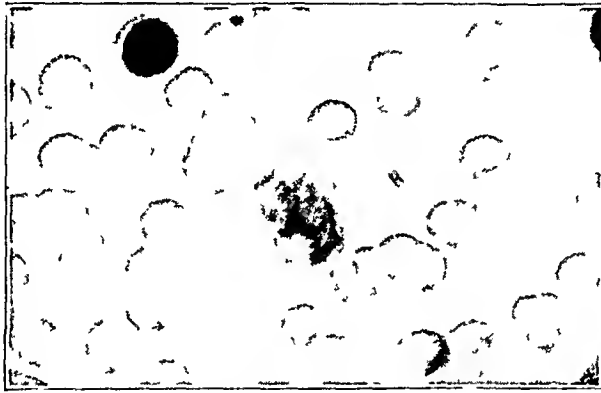


Fig 1—Blood smear. The large cell in the center is a myeloblast with an Auer body in its cytoplasm.

interpretation of the present case to consider in more detail the morphology of the cells as they appeared in the peripheral blood and in tissue sections.

In blood smears the cells were large, varying in diameter from 11 to 18 microns. The nucleus was large, usually occupying the greater part of the cell. In most cases the nuclear outline was irregular, there being one or more indentations, or the nucleus had an irregularly lobulated appearance, corresponding to cells of the Rieder type (Fig 1). In preparations stained with Wright's or Jenner-Giemsa stains, the nucleus contained a very fine meshed purplish network, in which there were no large clumps of chromatin. These cells differed from lymphocytes in the relative homogeneity and fine, thin skinned, almost granular

<sup>17</sup> Gorham, L. W. Acute Myelogenous Leukemia, Albany M. Ann. **38** 201, 1917.



structure of their nuclei. Several distinct, clear areas, usually referred to as nucleoli, were frequently present in the nucleus. The cytoplasm was basophilic, and usually had a lighter perinuclear zone or an area of lighter cytoplasm at the nuclear indentation. In these clear areas, and to a less extent throughout the cytoplasm, were varying numbers of azure granules, usually only a few. Auer bodies were seen in the cytoplasm of some of these cells. Except for the irregularity of their nuclei, the cells closely resembled the "lymphoidocyte" as depicted by Pappenheim<sup>18</sup>. With the oxidase stain, the azure granules and Auer bodies reacted positively.

In tissue sections the cells were equally characteristic. The nuclei presented the same irregularities in outline that were seen in the peripheral blood, although cells with round or oval nuclei were also present. The nuclei were clear, the nuclear membranes distinct, and a few



Fig 2—Section of splenic pulp, stained with azure II-eosin. The central cell contains an Auer body.

small chromatin particles were scattered throughout. One or two basic nucleoli, and in preparations stained with Goodpasture's stain, a distinct reddish nucleolar-like structure were seen in most of the cells. The cytoplasm was lavender, and sometimes contained an Auer body (Fig 2). These cells were easily distinguished from the lymphocytes by their clear, irregular nuclei, relatively devoid of chromatic material, and their distinctly less basophilic cytoplasm. It was equally easy to distinguish them from "stem cells," which have deeply basophilic (azurophilic) cytoplasm and large, clear, regular nuclei.

With the oxidase reaction, the myeloblasts showed large numbers of granules, and the Auer bodies, reacting positively, were rendered much more distinct (Fig 3).

<sup>18</sup> Pappenheim: *Hematologische Bestimmungstabellen*, Leipzig, Werner Klinkhardt, 1920.

From the above, it is apparent that the cells were not typical of any one type. In smears they differed from Pappenheim's "lymphoidocyte" only in the irregularity of the nucleus, from the monocytes, in the fineness of the chromatin network, the presence of several distinct nucleoli, and a perinuclear zone of lighter cytoplasm. In sections they differed from "stem cells" in the less basophilic character of their cytoplasm and the irregularity of the nucleus.

I believe that they were cells in the early stages of myeloid differentiation. Inasmuch as definite granules could not be demonstrated without the oxidase reaction (pathologic retardation?), they were not

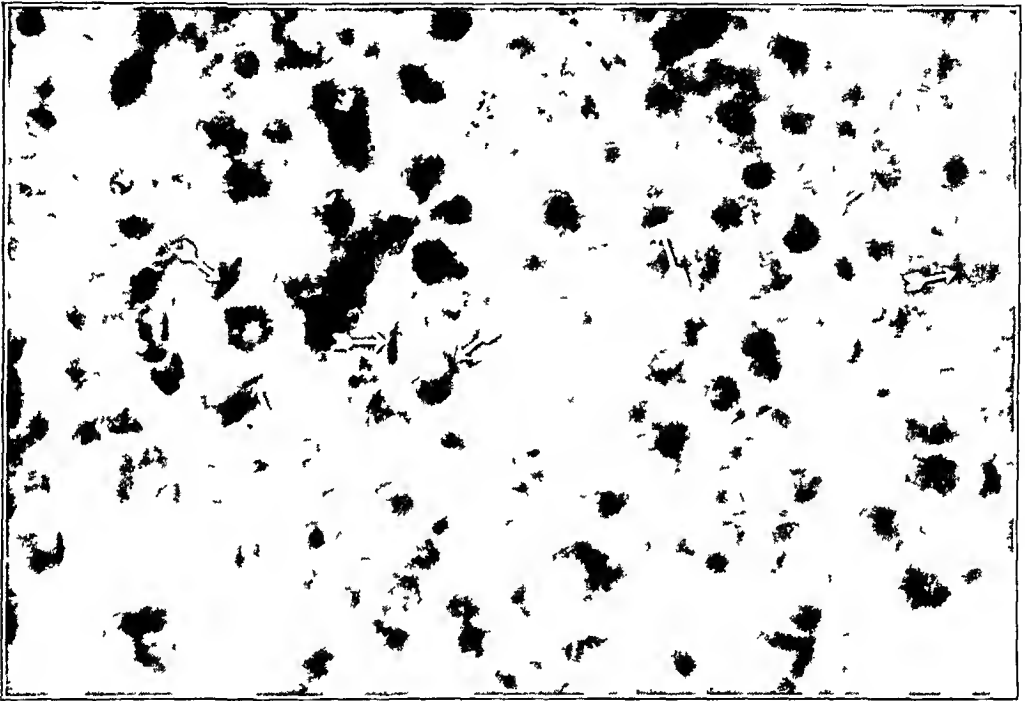


Fig 3—Section of splenic pulp, stained with oxidase stain. Some of the more prominent Auer bodies are indicated by arrows.

myelocytes, and are referred to in this paper as "myeloblasts," although it is realized that they were not identical with the "myeloblasts" of Naegeli.

*The Auer Bodies*—The Auer bodies in the present case did not differ from those previously reported. They were distinctly seen in fresh blood preparations as refractive rod-shaped bodies. In smears stained with Wright's stain, they appeared bright red. Jenner's stain did not stain them. They varied in length from 1 to 5.2 microns, and in width from very fine lines to 0.75 microns. The rods were not always of the same form, sometimes being thicker at one end than the other, or thicker in the middle than at either end. The ends were

sometimes rounded, sometimes pointed, sometimes square, the two ends not always being alike. Usually there was only one Auer body in a cell, occasionally two or three.

The Auer bodies were always in the cytoplasm, usually, but not always, tangential to the nucleus, and frequently lay in the deep nuclear indentation. Sometimes they were over or partially over the nucleus, but not within it. They did not lie within vacuoles. Occasionally a rod was seen in the vicinity of a disintegrated cell, and once in a myelocyte, but in no other instance were they free in the blood plasma or in any cells other than myeloblasts.

In tissue sections, the Auer bodies appeared about the same as in blood smears, i. e., they were of the same form and position. By the methods with which they were stained, they appeared bright red. The bodies appeared a little larger on the average (up to 6.8 microns) in oxidase preparations than in the others. The measurements in sections were taken on rods lying in the plane of the section, to avoid error. With the oxidase stain, the bodies appeared of the same homogeneous structure as the other oxidase granules, and there seemed to be all gradations in size from the granules to the rods. In other than oxidase preparations, however, the granules were not to be seen, and the shorter rods were either faintly stained or not at all.

The demonstration of Auer bodies in tissue sections has not thrown much light on their nature or origin. It does, of course, add another argument against their being artefacts. A body demonstrable in preparations of so many different kinds—fresh blood, blood smears and tissue sections—and by different stains and technical methods, can hardly be considered as such. Furthermore, they probably occur in only one type of cell (myeloblasts), only in one part of the cell (cytoplasm), and possibly in only one disease (acute leukemia)—this last, of course, if Roth's case and the present one may be so interpreted.

Ishikawa's investigations with bacteriologic stains and methods practically exclude them from the class of bacteria, and the absence of detailed structure, especially nuclear material, is against the possibility that they are parasites of some other type.

Special mitochondrial methods were not used. There are important differences, however, between mitochondria and Auer bodies, both morphologically and in their staining reactions. Most of the stains which are useful in demonstrating the Auer bodies contain azure, which is a poor mitochondrial stain.<sup>19</sup> Wallin<sup>20</sup> also found mitochondria stainable by pyronin-methyl green, which, according to Pappenheim, does not stain Auer bodies.

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<sup>19</sup> One azure containing mixture (Giemsa's stain) has recently been found by Cowdry and Olitsky to stain mitochondria little, if at all (*J. Exper. M.* **36**: 521, 1922).

<sup>20</sup> Wallin I. E. On the Nature of Mitochondria. III. The Demonstration of Mitochondria by Bacteriologic Methods. *Am. J. Anat.* **30**: 451, 1922.

That they are related to cell granules<sup>21</sup> is suggested by the presence of bodies of all intermediate sizes. Of these, then staining reaction most closely resembles granules of the methylene-azure group. In tissue sections, however, they are demonstrable by methods that do not stain the azure granules<sup>22</sup>

The globular bodies in the spleen and lymph node probably do not belong to the same class of substances as the Auer bodies. With Dominici's stain, they were purple instead of red, and appeared in plasma or lymphoid cells instead of in myeloblasts. Resembling, as they did, the "mulberry cells" of Weber, or the "fuchsin bodies" of Russell, it is more probable that they were some form of hyalin (Weber and Blendinger,<sup>16</sup> Goodpasture<sup>23</sup>). Furthermore, as previously shown, the fuchsin bodies were strongly gram-positive (Russell,<sup>24</sup> McConnell and Lang<sup>25</sup>) while the Auer bodies were not demonstrable by the Gram stain (Ishikawa)

#### SUMMARY

1 Auer bodies have been demonstrated in microscopic sections of a case that was probably one of acute myelogenous leukemia

2 The bodies are demonstrable in paraffin, celloidin and frozen sections, and by several stains

3 In the oxidase stain they react positively, both in blood smears and in tissue sections

4 Wright's blood stain, Giemsa's and Goodpasture's acid polychrome-methylene blue and eosin are very satisfactory for their demonstration. Dominici's stain and azure II-eosin stain them, but less distinctly. They were not stained by hematoxylin and eosin, Gabbett's stain, nor by Gram's method

5 Auer bodies have the same morphologic appearance in tissue sections that they have in blood smears

6 The Auer bodies were found within the cytoplasm of atypical myeloblasts, and, in blood smears, in the immediate vicinity of disintegrated cells. Only once was an Auer body seen in a myelocyte

7 The Auer bodies are not identical in staining reactions with any of the known normal cell granulations, nor with the hyaline bodies (Russell's fuchsin bodies) which were present in the same sections

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21 Elongated granules (rod or spindle shaped) occur normally in some of the lower vertebrates, as birds and reptiles

22 Azure granules were not seen in tissue sections except with the oxidase method, although Auer bodies were stained by other methods as well

23 Goodpasture. Crystalline Hyalin, J. M. Research **35** 259, 1917

24 Russell, William. An Address on a Characteristic Organism of Cancer, Brit. M. J. **2** 1356, 1890

25 McConnell and Lang. Russell's Fuchsin Bodies, J. M. Research **42** 99, 1920

# THE EFFECT OF SPLENECTOMY ON THE HEMOPOIETIC SYSTEM OF MACACUS RHESUS<sup>1</sup>

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The diversity of the reported results of splenectomy in different species of animals has been a striking feature in publications on this subject,<sup>1</sup> and has contributed to a rather widely held view that comparatively little is known in regard to the functions of the spleen. Nowhere is this fluctuation of opinions and prevalent agnosticism better shown than in the editorials of the *Journal of the American Medical Association*.<sup>2</sup> Recognizing that much still remains to be learned about the various functions of this complex organ, and (as is usually the case when advances are being made in any given field) that not a few observations by different investigators are at variance, nevertheless it should be recognized that material progress has been made, and in the relation of the spleen to blood formation and blood destruction, at least, a number of positive facts can be accepted, as we have tried to show elsewhere.<sup>1</sup>

These facts have chiefly been elicited by studying the structural and functional changes produced by the removal of the spleen either from normal or experimentally altered animals, and of administering hemolytic agents to animals that have had their spleens removed, ligated, or diverted from the circulation by a modified Eck fistula. The temporary anemia and leukocyte changes, the increased resistance of the erythrocytes to hypotonic salt solution, the lessened tendency of the organism to the production of hemoglobinuria and jaundice, the compensatory changes in the liver, lymph nodes and bone marrow, and the importance of the circulatory factor in bringing about these changes, are all items that have previously been commented on and that need not be more than mentioned at this moment.

Although our findings in the dog agreed fairly closely with the available data on man, nevertheless, they differed in several particulars from the results found by other investigators in the rabbit, cat and

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\* From the John Herr Musser Department of Research Medicine of the University of Pennsylvania and the Laboratories of the Philadelphia General Hospital.

\* The manuscript and slides have been placed in the National Depository at the Army Medical Museum, Washington, D C.

1 Pearce R M, Krumbhaar, E B, and Frazier, C H. The Spleen and Anemia, Philadelphia, J B Lippincott Company, 1918.

2 J A M A 59 1546 (Oct 25) 1912 77 1577 (Nov 12) 1921 77 1823 (Dec 3) 1921 78 1056 (April 8) 1922

guinea-pig We, therefore, have thought it advisable to study some of these changes in the monkey with the idea not only of obtaining comparative data in yet another species, but also that the results obtained from an animal more nearly related to man might give a more reliable basis for comparison with the study of the function of the human spleen

#### METHODS

The blood pictures of six monkeys (Nos 1, 2, 5, 6, 10 and 12) were followed over periods varying from six weeks to two years after splenectomy, with two nodectomized monkeys as control The response to a hemolytic agent was observed in four splenectomized monkeys and four controls, and the hemopoietic system of eight monkeys and controls studied post mortem The following items of the blood picture were studied hemoglobin,<sup>3</sup> erythrocytes, leukocytes, differential counts, reticulated erythrocytes, platelets and resistance of erythrocytes to hypotonic salt solution On account of numerous accessory factors that may influence the blood picture, such as age, feeding, emotion, exercise, etc, especial care was taken to standardize conditions as far as possible by having counts made at the same time of day, at the same interval after feeding, by the same operator, and with the same instrument, and using only healthy animals of as nearly the same age and size as the control as could be obtained At this point it should be noted that size and weight are not indications of age in this species, as we have had very small monkeys with correspondingly "young" teeth remain relatively unchanged in size and weight over periods of more than three years Two or more preliminary counts were made over periods varying between a week and three months before beginning the experiment In spite of these precautions, variations were occasionally obtained so much greater than the limits of error of the methods employed, that they must be attributed to other unknown factors not controlled or to individual differences in response Unlike the domestic animals previously used, most of the monkeys tended to lose some weight under laboratory conditions, but this loss proved no greater in the test animals than in the normal controls, and was surprisingly independent of the severity of the anemia Tuberculosis did not prove to be a disturbing factor

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3 Hemoglobin estimations were begun with a Sahli instrument that happened to check closely with simultaneous determination of the oxygen capacity of the blood Later the Newcomer method was also used, but for the sake of uniformity only the Sahli figures are given Though the Newcomer glass was also checked with the oxygen capacity method it tended to give lower readings, and differences between the two methods fluctuated for reasons that we have been unable to ascertain

## RESPONSE TO SPLENECTOMY

The results of simple splenectomy we have found to be less marked in the monkey than in either man or dog, but of the same nature. A moderate anemia<sup>4</sup> began almost immediately after operation, although on the first day or two a slight rise in the blood picture was noted in two cases. While this rise is hardly beyond the limit of accuracy of

TABLE 1—ERYTHROCYTE COUNTS AFTER SPLENECTOMY (IN MILLIONS)

	Monkey 1	Monkey 2	Monkey 5	Monkey 6	Monkey 10	Monkey 12	Monkey 11
Relative spleen and body weight	0.09%	0.09%	0.14%	0.16%	0.18%	0.08%	Control Nodectomy
Before splenectomy	6.40	7.14	6.80	6.14	5.60	5.14	5.86
Before splenectomy	5.90		5.90	6.03	5.20	4.99	5.76
1 day after	5.49	5.89	5.03	5.88	5.50	5.29	5.84
3 days after			4.10	5.53	4.43	4.88	5.93
5 days after				4.91		5.04	5.55
7 days after	5.56	6.12	4.55	4.89	4.80	4.75	5.78
9 days after				4.69	4.48	5.02	5.68
14 days after	5.17	5.20	5.09		4.95	5.39	5.56
21 days after	6.03	5.82	5.51	5.09		5.36	
28 days after	6.10	5.41	5.55	5.09		5.25	
35 days after	6.58	5.55		5.13		5.52	
42 days after	6.37	5.94	5.60	5.40		6.34	
2 months after	6.10	5.50	6.06	6.23	5.16	5.56	
3 months after			5.89	6.10			
4 months after	6.50	4.90	6.19	6.16			
12 months after	Killed	Killed	6.04	5.90	6.35	6.4	
15 months after			6.40	6.26	6.30	6.0	6.00
24 months after			6.44	6.02	6.16	6.16	6.51

TABLE 2—HEMOGLOBIN ESTIMATIONS AFTER SPLENECTOMY

	Monkey 1	Monkey 2	Monkey 5	Monkey 6	Monkey 10	Monkey 12	Monkey 11
Before splenectomy	98	102	92	98	102	97	90
Before splenectomy	94		85	92	98	97	92
1 day after	83	86	75	88	105	88	94
3 days after			71	86	86	86	92
7 days after				82		90	90
9 days after	91	85	78	86	94	84	95
14 days after	73	83	85	85	88	86	102
21 days after	86	93	90	81	100	96	86
28 days after	100	94	93	85		98	
35 days after	102	96		92		88	
42 days after	103	101	103	98		100	
2 months after	99	97	99	100		102	
3 months after			97	101		96	
4 months after	100	83	102	96	100		
12 months after	Killed	Killed	93	86		96	
15 months after			103	92	91	91	92
24 months after			108	92	88	92	98

the method, we think it is probably to be explained by some such factor as a greater concentration due to postoperative change in blood volume. The greatest degree of anemia, which, however, never reached a point lower than four million cells per cubic millimeter and 71 per

<sup>4</sup> For the blood picture of normal monkeys under our laboratory conditions see J. M. Research, 42:105, 1921.

cent hemoglobin, was reached in the first two weeks and the return to normal was accomplished before the second month. There was no subsequent noteworthy polycythemia, such as was reported in some of the early dogs studied. No essential difference was noted between the hemoglobin and erythrocyte curves. As controls, two monkeys were used, on which laparotomies were performed, the spleens handled, and an abdominal lymph node removed. From the example given in the table, it will be seen that no anemia resulted in spite of these procedures and of frequent taking of blood samples. Estimations of blood volume by the vital red method of Keith, Rowntree and Geraghty in the postsplenectomy anemia of dogs show that there are actually fewer corpuscles in the vascular system and not merely a lessened concentra-

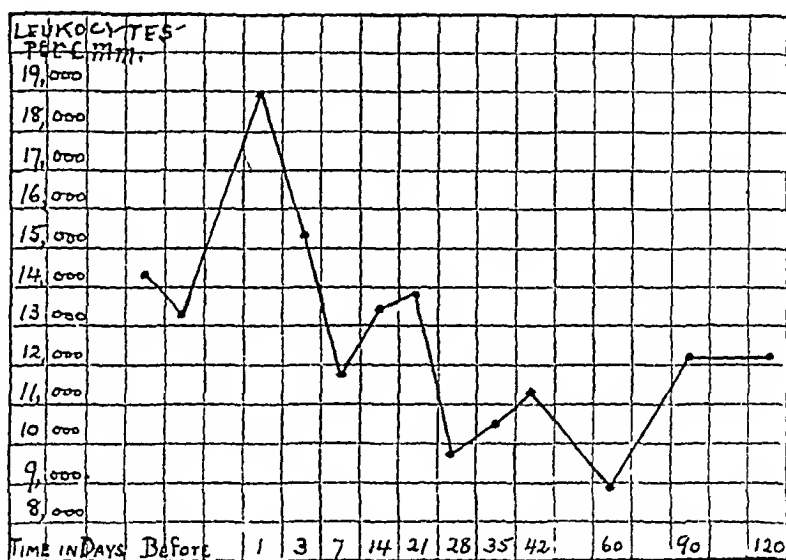


Chart 1—Leukocyte count in splenectomized monkeys. Composite curve based on six test monkeys.

tion due to hydremia. It did not prove feasible to carry out similar tests on the monkeys of this series.

The resistance of the erythrocytes (which before splenectomy averaged complete hemolysis at 0.33 per cent sodium chloride and beginning hemolysis at 0.45 per cent) was increased in every splenectomized animal. This was usually evident on the first or third day after operation and continued during the period of observation. Averages in six splenectomized monkeys showed that the increase was maintained during the period of observation and reached a maximum complete hemolysis at 0.26 per cent and beginning hemolysis at 0.42 per cent. This striking increased resistance of the erythrocytes, persisting over such a long period, confirms our previously expressed view that it constitutes one of the most important results of splenectomy. Its occurrence in disease



the nonanemic splenectomized monkey, whose erythrocytes were also the most resistant, showed the most marked anemia and the longest period of repair. Although it is obvious that no conclusions can be drawn from such discordant results, they are recorded as instances of the complexity of the problem, with the suggestion that possibly the variations may be brought about by the two factors (loss of spleen and resistance of erythrocytes) operating to different degrees in different

TABLE 3—RESPONSE TO HEMOLYTIC AGENT, 0.2 GM SODIUM OLEATE  
BEING GIVEN INTRAVENOUSLY

Resistance to Salt Solution	Monkey 5 Splenectomy, 7 Weeks, C H 0.26, B H 0.42		Monkey 10 Splenectomy, 2 Weeks, C H 0.30, B H 0.42		Monkey 14 Normal, C H 0.34, B H 0.46	
	R B C	Hgb	R B C	Hgb	R B C	Hgb
Before sodium oleate	55	85	50	80	56	78
1 day after	62	76	39	67	49	72
2 days after	56	80	37	59	49	76
4 days after	58	88	44	70	53	75
6 days after	58	81	45	81	51	82
9 days after	60	96	46	80	55	84
11 days after	66		50	84	58	84
14 days after	59	81	44	88	54	84
16 days after	57	81	42	82	54	86
Greatest drop		9	13	21	07	6

TABLE 4—RESPONSE TO HEMOLYTIC AGENT, 0.15 GM SODIUM OLEATE  
BEING GIVEN INTRAVENOUSLY

Resistance to Salt Solution	Monkey 1 Splenectomy, 17 Weeks, C H 0.28, B H 0.46		Monkey 6 Splenectomy, 9 Days, C H 0.34, B H 0.44		Monkey 11 Normal, C H 0.32, B H 0.44	
	R B C	Hgb	R B C	Hgb	R B C	Hgb
Before sodium oleate	65	100	47	85	55	95
1 day after	634	100	50	78	56	90
2 days after	63	88	46	74	57	94
4 days after	48	88	42	72	49	86
6 days after	52	90	46	75	49	86
9 days after	48	90	49	79	53	92
13 days after	50	96	51	81	54	90
15 days after	50	94	54	89	55	95
21 days after	57	94	51	92	56	94
Greatest drop	154	12	05	13	06	9

subjects. It is apparent from these experiments that the toxicity of sodium oleate for monkeys is too great to permit sufficient latitude for its profitable use as a hemolytic agent.

#### PATHOLOGY

Opportunity to study changes in the viscera after splenectomy was offered in five monkeys (Nos. 1, 2, 5, 6 and 10) with three others as controls (Nos. 4, 8 and 13). The high cost of monkeys since the war prevented the others from being sacrificed for this purpose. In

two of the five (Nos 1 and 5) biopsy specimens of bone marrow had been removed, one at the same time as the spleen, the other ten weeks after splenectomy, and in two other cases (Nos 11 and 12) abdominal lymph nodes were removed as operative controls. Of the five splenectomized monkeys, two monkeys (Nos 1 and 2) were killed by overdoses of sodium oleate five and four months, respectively, after splenectomy, and the third monkey was sacrificed two years after splenectomy, having been normal for a long period. For both the oleate monkeys death came suddenly while the injection was in progress, from causes that we could not establish, but certainly not from excessive blood destruction. Except for a few erythrocyte bearing phagocytes

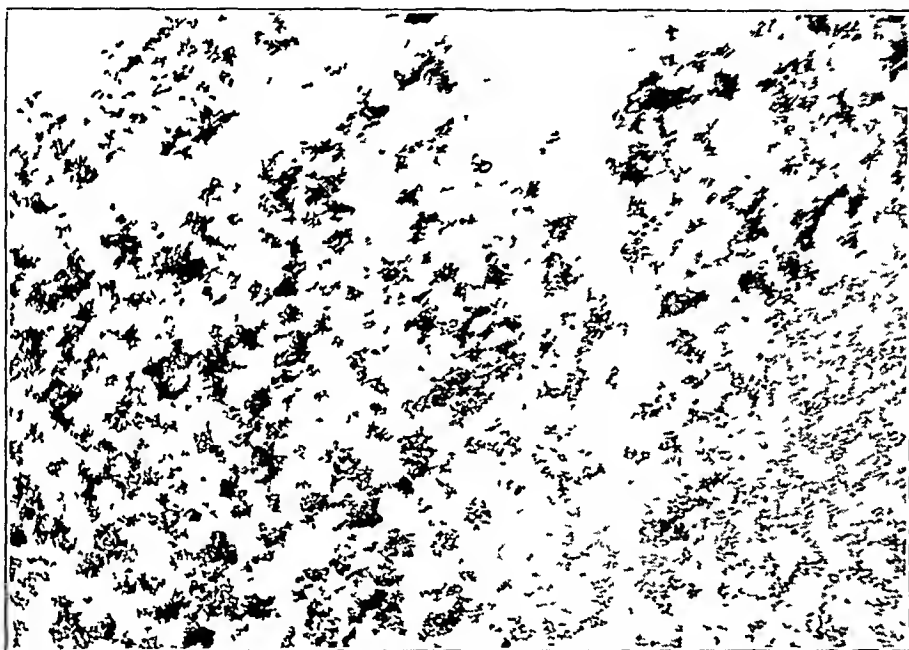


Fig 1—Bone marrow (Monkey 1), removed at biopsy, ten weeks after splenectomy  $\times 65$

in one lymph node, the post-mortem findings were those that we have customarily found after uncomplicated splenectomy. One monkey (No 5), though normal during life, at the necropsy was found to have the bone marrow studded with lymphoid follicles, an observation that has been reported by one of us elsewhere<sup>6</sup>. One monkey (No 10) was chloroformed while in good health, twenty-seven months after splenectomy. We shall consider these four animals together, with the reservations that the above facts necessitate. One monkey (No 6) died of generalized tuberculosis, apparently developing sometime after the conclusion of the experimental work, thus becoming useless for this study, and one monkey (No 12) still lives.

is probably in the same way one of the chief beneficial factors in those primary blood diseases that are helped by splenectomy<sup>5</sup>

That the anemia is due to lessened blood formation is indicated by the absence of normoblasts and Howell-Jolly bodies in the blood smear and almost complete disappearance of reticulated erythrocytes, which, however, are usually not more than 0.1 per cent in the normal monkey. The changes in the platelet counts were inconstant and never beyond the wide variations that are usually found in counting these elements

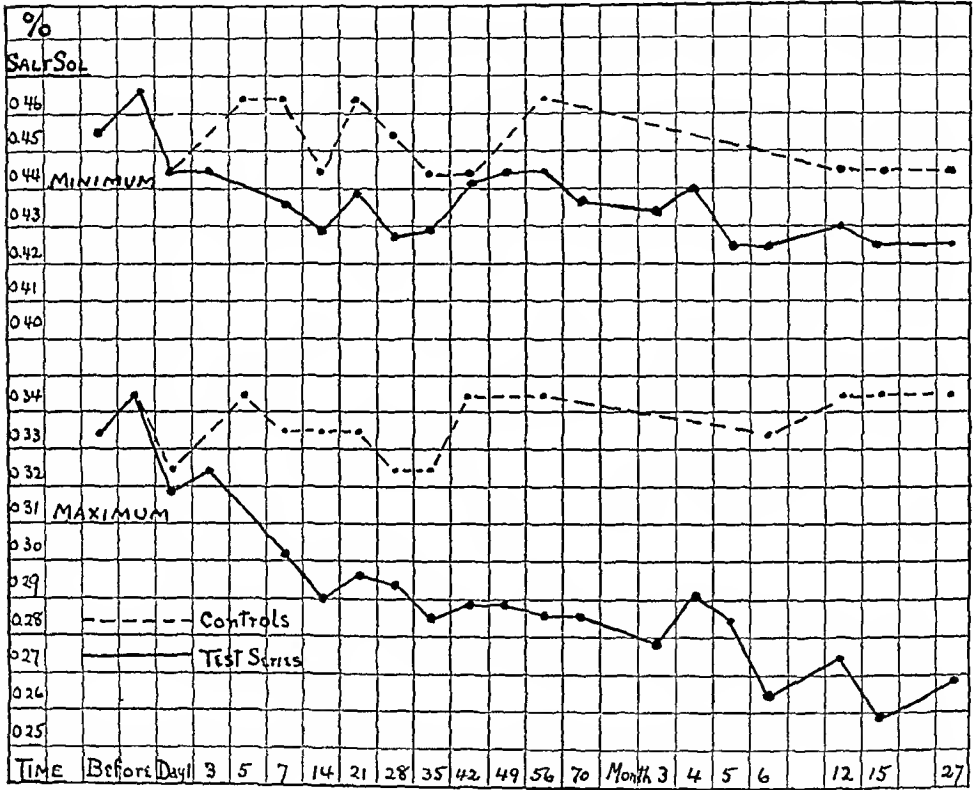


Chart 2—Resistance of erythrocytes of splenectomized monkeys. Composite curve based on estimations on six test monkeys and two controls. Upper solid line, minimum resistance of test monkeys, dotted line, controls. Lower solid line, maximum resistance of test monkeys, dotted line, controls.

under normal conditions. At any rate, there were no signs of a “blood crisis,” such as is frequently observed after removal of the diseased spleen of man. We have previously suggested that the anemia may be due to a loss with the spleen of a substance having a stimulating action on the erythrogenetic centers of the bone marrow, but we have no further evidence at present to support this view. The urobilin

<sup>5</sup> A discussion of the various views as to the cause of this increased resistance will be found on page 50 et seq. of our book on the spleen and anemia.<sup>1</sup>

excreted in the feces, as estimated by the Wilbur and Addis method, was so small that it was obviously impossible for splenectomy to produce any changes that would be beyond the limits of error of this method, and we, therefore, were without quantitative criteria of the amount of blood destruction

The total leukocyte count of the monkey, which in our series, averaged 14,200 per c mm before splenectomy was only raised a few thousand by the operation (to an average of 19,300 per c mm), and by the end of a week had fallen below the normal level. This is in marked contrast to the greater and more persistent rise that occurs in man and in the dog. The differential count, however, showed constantly both a relative and absolute increase in the number of polymorphonuclears and a decrease in the number of lymphocytes, a condition that returned approximately to normal in from two to three months. In the counts made more than a year after splenectomy, the lymphocytes were definitely increased. Taken with the increase in size and number of lymph nodes that we have observed in the splenectomized monkey post mortem this would indicate that the lymphoid rôle of the spleen is relatively more important and its erythrolytic function less important in the monkey than in the dog and man.

#### RESPONSE TO HEMOLYTIC AGENT

As a hemolytic agent, toluylendiamine was first tried in doses equivalent to those previously used successfully with dogs. The insignificant amount of hemolysis produced confirms the experience of other investigators that different species show considerable variations in resistance to this drug. Sodium oleate was next given to two groups of monkeys, each group made up of a monkey anemic after splenectomy, one that had recovered from his anemia and a normal control. What proved with three monkeys to be a lethal dose (Nos. 1, 2 and 4, 0.2 gm per kilo injected intravenously over a period of fifteen minutes) in others only caused hemoglobinuria for a few hours, without subsequent choluria, and produced a mild anemia that lasted about two weeks. An increase of both maximal and minimal resistance of the erythrocytes, amounting to from 0.4 to 0.8 per cent sodium chlorid, was noted in all but one monkey receiving sodium oleate. As most of these had recently been splenectomized, however, no deductions can be made from this observation. In this group, the anemic splenectomized monkey (No. 10) showed the greatest loss of blood and longest period of repair, but the nonanemic splenectomized monkey (No. 5) whose erythrocytes were the most resistant of the three, showed even less effects from the oleate than the normal control (No. 14). In the other group (receiving 0.15 gm per kilo of sodium oleate)

*Bone Marrow*—In the bone marrow removed coincident with the spleen of the control monkeys, a pink or even splotched reddish appearance was found by histologic examination always to be due to more or less congestion, the hemopoietic cellular content being slight, and never filling more than from 10 to 40 per cent of any given area. Estimation of the amount of bone marrow hyperplasia is made very difficult by the great variation that occurs often in closely adjacent areas. An attempt was made to cover this difficulty by considering the extremes as well as the general appearance. Definite leukogenetic and erythro-genetic islands in Bunting's sense were impossible to distinguish, though

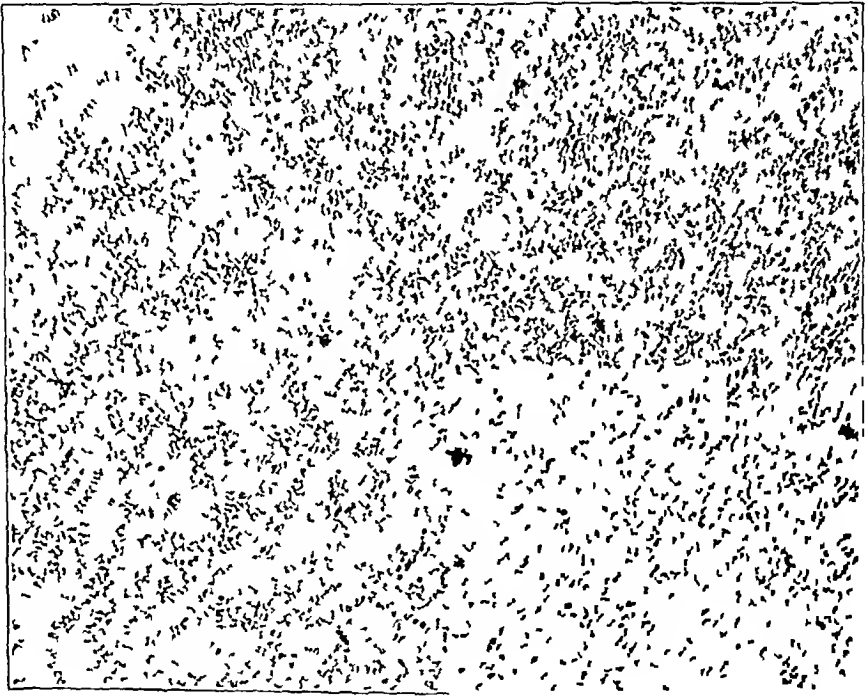


Fig 2—Bone marrow (Monkey 1) at necropsy, four and a half months after splenectomy  $\times 92$

there was, at times distinct clumping of the normoblasts. In the bioptic bone-marrow of monkey 5, the polymorphonuclears and normoblasts were especially prominent, with the other customary bone marrow cells approximately in their usual proportions. A small amount of hemosiderin pigment was found contained within phagocytes in about the same amount as is found in normal spleens. No mitosis was found.

In the bioptic bone marrow of the monkey splenectomized after ten weeks (No 1), the cellular areas never exceeded 20 per cent of the field. Hemopoietic cells were found in the following proportions: Mononuclear cells (primordial cells myeloblasts, myelocytes, histiocytes [?]), 55 per cent, polymorphonuclears, 28 per cent, normo-

blasts, 12 per cent , megaloblasts, 2 per cent , eosinophil myelocytes, 1 per cent , eosinophil leukocytes, 1 per cent , giant cells, 1 per cent , in other words a predominance of immature leukogenetic and possibly of nonhemopoietic cells

At necropsy, the bone marrow hyperplasia of the splenectomized animals was found to be always present and distinctly greater than the controls, from 70 to 95 per cent of large areas being filled with hemopoietic cells. For instance, in monkey 1, killed four and one-half months after splenectomy, the bone marrow was a deep reddish pink and cells occupied more than 95 per cent of many areas, in the follow-

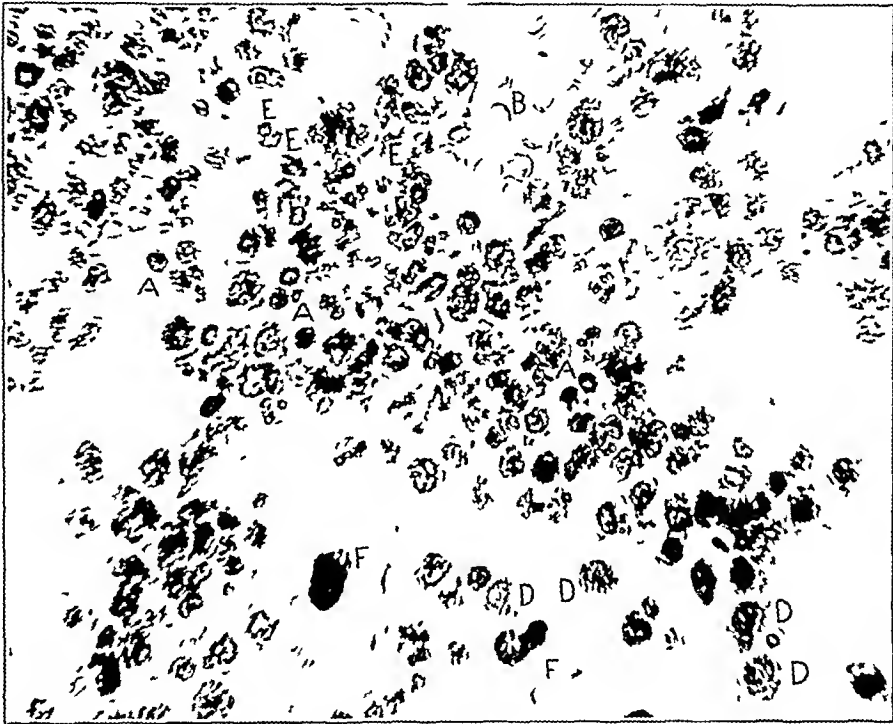


Fig 3—Bone marrow (Monkey 1), oil immersion,  $\times 600$  Note a, normoblasts, b, erythrocytes, d, myelocytes, e, polymorphonuclears, f, phagocytes with pigment, etc

ing proportions. Mononuclear cells, 24 per cent , polymorphonuclears, 45 per cent , normoblasts, 22 per cent , eosinophilic myelocytes, 2 per cent , eosinophilic leukocytes, 2 per cent , lymphocytes (?), 1 per cent , mononuclear giant cells, 1 per cent , multinuclear giant cells, 2 per cent , megaloblasts, 1 per cent. The site of the previous operation was filled in with new bone, the cavity being filled with orange colored gelatinous material and loose bone spicules. The marrow of monkey 2, killed four months after splenectomy, showed a somewhat larger percentage of polymorphonuclears, and greater variations in the cellular content of different areas. In the other two monkeys (Nos 5 and 10) the hyperplasia was not so marked, being about 80 and 70 per cent in

most fields, but in a few areas reaching as low as 40 and 10 per cent, respectively. This decrease was apparently chiefly due to a lesser number of polymorphonuclears. In the control bone marrows the cellular areas occupied from 10 to 40 per cent of the whole, with a larger number of immature forms. For instance, the bone marrow of monkey 8 (cause of death undetermined), though deeply congested like the other organs, microscopically was from 10 to 40 per cent cellular, in these proportions: mononuclear cells, 66 per cent, polymorphonuclears, 10 per cent, normoblasts, 20 per cent, eosinophil myelocytes, 1 per cent, eosinophil leukocytes, 1 per cent, giant cells, 2 per cent. Mitosis was only found a few times in the marrow of one of the

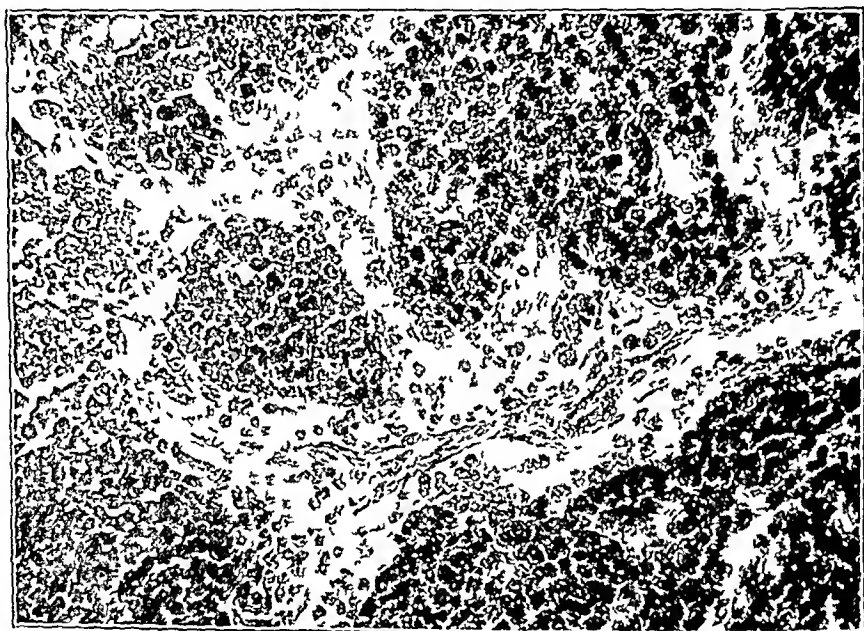


Fig 4—Lymph node (Monkey 1), at necropsy, four and a half months after splenectomy.  $\times 276$ . Note the sinuses moderately filled with phagocytes, many of which contain hemosiderin pigment.

splenectomized animals. Hemosiderin pigment—both intracellular and extracellular—was found somewhat more commonly than in the controls.

These results confirm the findings of Pearce and Pepper,<sup>7</sup> with the difference that in these long time splenectomies there was no exception to the development of cellular hyperplasia. Leukogenesis and erythrocytogenesis may both be said to have been active, though to different degrees in the different animals. On the whole, myelocytes and undifferentiated mononuclear forms were relatively more frequent in the controls than in the splenectomized animals. It should be borne in mind, also, that

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<sup>7</sup> Pearce R M, and Pepper, O H P. The Changes in the Bone Marrow After Splenectomy, *J Exper M* 20 19, 1914.

there is no definite criterion for some of the hemopoietic cells and many in the hyperplastic areas may have been concerned, not with hemopoiesis, but with the utilization of iron or other activities, taken over in the absence of the spleen

*Lymph Nodes and Kupffer Cells of Liver* —The mesenteric, gastro-hepatic and prevertebral lymph nodes of five splenectomized and four control monkeys were studied at necropsy, and in three cases nodes obtained at biopsy were also available. In two cases, nodes from all parts of the body were examined, without obtaining any additional information, in one case tuberculosis and in two cases camphorated oil lesions masked the picture. In all the splenectomized monkeys the visceral lymph nodes seemed abnormally prominent, and on microscopic

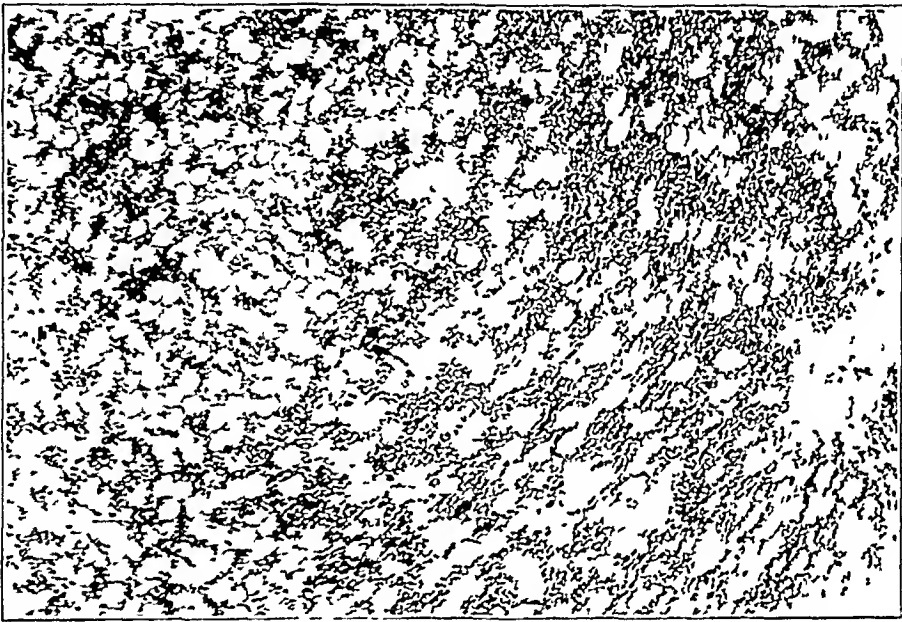


Fig 5—Bone marrow (Monkey 2), animal killed four months after splenectomy  $\times 69$

examination the large mononuclear cells of the sinuses (endothelial leukocytes, macrophages, etc) were distinctly increased over the normal, although the amount of pigment contained in them was no greater than was sometimes found in presumably normal nodes of the controls (No 4). Neither was any phagocytosis of erythrocytes observed, nor would such be expected in the absence of any acute, severe hemolytic process. In spite of the most careful search, no hemolymph nodes could be found. In a few cases, nodes were found that were dark red at one end, but this was always found on microscopic examination to be due to congested vessels within the follicles or sinuses, and at most only a few scattered erythrocytes were free in the lymph sinuses. In the two monkeys (Nos 1 and 2) that died during the administration



of sodium oleate, the macrophages were markedly increased, and a considerable number contained hemosiderin pigment or showed a cytoplasm of a peculiar coppery appearance, but never contained erythrocytes, so that the causative action of the oleate is problematical

The stellate endothelial cells (Kupffer cells) of the liver likewise seemed to be more numerous and prominent in the splenectomized monkeys than in the controls. They contained more or less hemosiderin pigment (as did one of the controls, No 4), but in no case was this extreme or were erythrocytes found within the phagocytes. In one monkey (No 10) hemosiderin, and probably hemofuscin, were also found scattered as fine granules through the liver cells. A similar picture has been reported in hypertransfused rabbits<sup>8</sup>. Examination of other organs revealed nothing pertinent to this study.

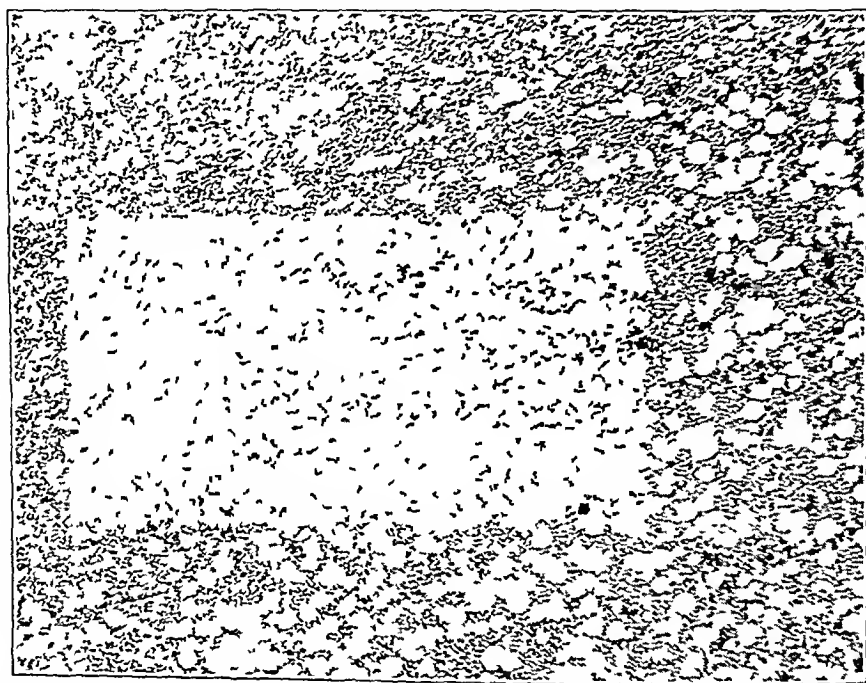


Fig 6—Bone marrow (Monkey 10), animal killed two years after splenectomy  $\times 69$ . Note the very marked cellular hyperplasia.

These findings, both in lymph nodes and in the Kupffer cells, are in accord with Pearce and Austin's previous studies<sup>9</sup> on dogs and confirm their suggestion that in splenectomized animals these organs, together with the bone marrow, take over, or at least develop to a greater extent, the part played by the spleen in the disposition of effete erythrocytes and their disintegration products.

8 Krumbhaar, E. B., and Chanutin, A. Studies in Artificial Plethora, *J. Exper. M.* **35** 847, 1922.

9 Pearce, R. M., and Austin, J. H. Changes in the Endothelial Cells of the Lymph Nodes and Liver of Splenectomized Animals Receiving Hemolytic Serum, *J. Exper. M.* **16** 780, 1912.

## DISCUSSION

It is obvious that while the results of removing the monkey's spleen are less marked than in the case of dog or man, they tend in the same direction, as opposed to the negative findings in rabbit and guinea-pig. In searching for possible explanation of these differences, the relation of the weight of the spleen to the body weight was compared in the different species. In twenty-three normal dogs, we have found that the spleen averaged 0.25 per cent of the body weight, and in seven normal monkeys the spleen averaged 0.13 per cent, with variations between 0.09 and 0.18 per cent. Figures given by Welcker and Brandt<sup>10</sup> for the other species are: man, 0.25 per cent, guinea-pig, 0.13 per cent, rabbit, 0.05 per cent. It would, therefore, be logical to expect that splenectomy would produce less results in the species with the relatively smaller spleens, especially as it is believed that the spleen is only one of several elements in the hemopoietic system, and that other elements may acquire the ability to compensate for its absence. In our monkeys, the most marked change occurred in those that had had relatively larger spleens, though it must also be recognized that the initial resistance of the erythrocytes was also a factor. This hypothesis is further supported by Wolferth's<sup>11</sup> observations that the same changes occur in the albino rat after splenectomy that we found in dogs<sup>12</sup> and that in eight rats with abnormally large spleens the changes were even more marked and proved fatal in seven.

## RESULTS

1 In the *Macacus Rhesus*, splenectomy produces an anemia that is much less marked than in the case of dog or man. The resistance of the erythrocytes is increased throughout the period of observation.

2 The number of reticulated erythrocytes is diminished and no signs of a "blood crisis" are to be found.

3 The total leukocyte count is only slightly increased during the first week, but an absolute and relative increase of polymorphonuclears and decrease of small lymphocytes persists for a longer period.

4 The *Macacus Rhesus* is resistant to toluenediamine hemolysis. Sodium oleate causes an anemia that may be more severe and last longer in the splenectomized animal, but greater resistance of the erythrocytes may apparently outweigh the loss of the spleen.

5 The bone marrow is very little, if at all, hyperplastic at early periods after splenectomy, but by the fifth month, cellular hyperplasia is marked and continues so to the latest period of observation (twenty-seven months).

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10 Welcker H, and Brandt, A. Arch f Anthropol **28** 37, 1902.

11 Wolferth, C. C. Arch Int Med **19** 105 (Jan) 1917.

12 Relation of spleen to body weight of albino rat—0.25 per cent, according to Wistar Institute statistics.

6 The visceral lymph nodes are more prominent after splenectomy, and phagocytic action more marked. Hemolymph nodes were not found.

#### CONCLUSIONS

1 Therefore it appears that the transient postsplenectomy anemia results chiefly, or, perhaps, wholly from lessened blood formation perhaps, due, as we have previously suggested, to the loss with the spleen of a substance which normally stimulates the bone marrow.

2 The persistent increased resistance of the erythrocytes is probably one of the most important results of splenectomy from a therapeutic point of view.

3 The histologic changes in the lymph nodes, bone marrow, and Kupffer cells of the liver of splenectomized animals indicate that these organs take over the spleen's share in disposing of effete erythrocytes and their disintegration products.

4 The different response of various animal species to splenectomy is at least partly explained by the difference in the relative spleen and body weights in the various species.

# THORACOPLASTIC COMPRESSION OF THE LUNG IN PULMONARY TUBERCULOSIS \*

PHILIP KING BROWN, M D

AND

LEO ELOESSER, M D

SAN FRANCISCO

## I MEDICAL ASPECTS (PHILIP KING BROWN)

There is but one therapeutic agency in the treatment of tuberculosis that has stood the test of all time, and that is rest. For many years the technic of rest has been studied and notable contributions to it have come into general use. A few are in the developmental stage and deserve study and trial in well selected cases. The five methods in addition to rest in bed which have been proposed for producing relative immobilization of all or part of one side of the lungs are (1) (a) Postural rest, lying twenty-three and one-half hours a day on the affected side in one-sided cases, advocated by Webb (b) Sand bags on the affected part (Sewell), giving, to less degree, the same result (2) Section of the phrenic nerve in the neck on the affected side, causing paralysis of one half of the diaphragm and partial collapse of the lower lobe (3) Local replacement by some foreign body of the area occupied by the affected part of the lung if in the apex, after extrapleural rib resection (Tuffier) (4) Collapse of the lung by nitrogen gas or air introduced into the pleural cavity under pressure (Forlanini, 1882, Murphy, 1898) (5) Resection of all the parts on one side, causing thereby a narrowing of the chest on the affected side commensurate with the collapse needed (Friedrich, Wilms, Sauerbruch, etc.)

The first method is so simple that it demands trial in every unilateral process. So great has been Webb's success with the method that it has largely replaced artificial pneumothorax in his hands. In his exhaustive article on the subject<sup>1</sup> he presents roentgen-ray plates showing how limited is the motion on the side on which the patient lies and the exaggerated excursion of the upper side. The object of the fifteen minute periods on the well side is to facilitate cavity drainage.

Of resection of the phrenic nerve it has been said by Morrison Davies that it is especially applicable when there are secondary changes, either mechanical or from infection to considerable extent in the lower

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\* From the Division of Surgery, Stanford University Medical School

\* Read before the Fifty-First Annual Meeting, Medical Society of the State of California, May, 1922

<sup>1</sup> Webb. Tr. National Tuberculosis Association, 12 182, 1916

lobe, when it is advisable to diminish the movement of the lower lobe when it is the seat of primary disease, to prevent aspiration of tuberculous or pyogenic material from the upper lobe cavity, and as a preventive measure against the development of bronchiectasis in chronic interstitial pneumonia

Tuffier's procedure of partial thoracoplasty and introduction of foreign matter to aid compression, practiced also by Baer, has been used by numerous surgeons as an adjunct to extensive thoracoplasty, Archibald uses it in anterior apicoplasty, leaving the first rib intact, and feels that the shoulder is better supported in this way. Our own experience has been entirely with the efforts to bring about complete compression of the apex by removal of all or part of the first rib and shortening the clavicle

There remain to be considered the two means of complete collapse of the affected side, artificial pneumothorax and thoracoplasty

That pneumothorax has been a great contribution to the treatment of unilateral pulmonary tuberculosis, no one who has used it will deny. Like all therapeutic methods it had to go through a long experimental period, and doubtless its use has been abused badly. Too early cases in which there has been no trial of rest in bed in favorable surroundings, have undoubtedly been used to exploit the method. Too advanced cases offer only the palliative conditions following a lessened septic absorption. It is not a remedy to be used, except when the size of a cavity indicates the unlikelihood of closure if left to nature, although it is truly wonderful how much nature alone can do. A heart may be pulled over 2 or 3 inches, the diaphragm may retract several inches, the mediastinum contributes its bit by allowing considerable pushing over by the lung that is doing all the work, the shoulder on the affected side droops forward and in the roentgenogram the ribs are seen to be much closer together than on the good side. All this may not close a cavity or arrest activity, and even this much can only be accomplished when the pleuropulmonary fixation by adhesions assists the pulmonary fibrosis. Is it not obvious that anything which would assist the progress of fibrosis is to be encouraged? It is rarely the case that a lung in which retraction has gone on to a considerable degree is free from pleural adhesions and these adhesions are many times the reason that pneumothorax fails. Numerous illustrations of how they operate to hold cavity walls from collapse are to be found in any series of plates taken after this procedure. It is sometimes possible after repeated small injections of air to tear away small bands of adhesions or so to stretch them so that almost complete collapse follows. Jacobaeus of Sweden has introduced the use of an instrument akin to a large cystoscope and has met the difficulty of adhesions by opening the pleural cavity after such collapse as was

possible by artificial pneumothorax and cutting the restraining bands. How relatively easy this might be is illustrated by several of our cases, and while we have not as yet attempted it, we are convinced that in cases with few but effective adhesions successfully holding open a cavity, a trial of it is necessary as a step clearly indicated before thoracoplasty. That one is confronted with the danger of exciting a pyopneumothorax must be considered, for a cavity near the surface of the lung is often protected by a very thin wall and the release of a number of adhesions under pressure might easily put sufficient strain on the remainder to cause some giving way of the wall and the discharge of the cavity content into the pleural cavity.

That thoracoplasty is to be regarded as an ideal rest to a part that has reached a point where nothing else can affect the process, follows as a logical conclusion, and as the work has progressed in our hands, it has become more and more plain that when a lung is advanced in disease and pneumothorax is tied, thoracoplasty should follow if for any reason pneumothorax does not put the lung at rest.

## II SURGICAL ASPECTS (LEO ELOESSER)

It has been interesting to follow the changes in the points of surgical attack on pulmonary tuberculosis. Krause<sup>1a</sup> mentions the practice of artificial pneumothorax by the Hippocratic school. Sauerbruch<sup>2</sup> cites Willis as having cured tuberculous cavities in the seventeenth century by making a "fontanella" over the diseased side. Whether he opened the cavity or made an artificial pneumothorax is not apparent. In 1696, Baglivi wrote of introducing medicaments into "incurable internal ulcers of the lung" through an intercostal incision. In the eighteenth century a number of surgeons opened cavities with a lancet or trocar. These, I suppose, were cold abscesses from perforated cavities. In the eighties a number of authors resected portions of tuberculous lungs, and MacEwen<sup>3</sup> had a few brilliant results after the extirpation of entire purulent lobes.

With the exception of the ancient inductors of pneumothorax, and Willis with his "fontanella" over the diseased side, these surgeons were evidently following blind leads. Tuberculosis never makes an isolated tuberculoma of the lung; its lesions are diffuse. It is useless to remove one tuberculous patch and to leave many others behind.

Modern efforts to alter mechanically the course of pulmonary tuberculosis are based on observations of the effect of accidental complications (spontaneous pneumothorax and a pleuritic exudate) on the

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1a Krause. *Tr. Am. Climatol. & Clin. Assn.*, Thirty-Ninth Annual Meeting, Washington, D. C., 1922, *Am. Rev. Tuberc.* **6**: 154 (April) 1922.

2 Sauerbruch. *Chirurgie der Brustorgane*, Ed. 2 **1**: 591.

3 MacEwen. *Cavendish Lecture*, *West Lond. M. J.* **11**: 163 (July) 1906.

primary disease. A number of clinicians<sup>4</sup> had noted that neither pneumothorax nor an exudate were always untoward accidents, but that both sometimes arrested the underlying pulmonary disease. Spaeth,<sup>5</sup> in 1850, explained their benefits as being due to relaxation and immobilization of the lung. It was also a common observation that a chronic fibrous phthisis, with shrinkage of the lung, contraction and rigidity of one side of the chest, and displacement of the viscera toward the affected side, took a benign and slow course. To translate these two beneficial accidents, external compression of the lung, on the one hand, and internal shrinkage on the other, into practice was but a step. And yet, even after that sound basis had been established, the evolution of the present surgical procedures was by no means straightforward.

Forlanini,<sup>6</sup> in 1882, was the first to advocate imitation of a spontaneous pneumothorax by an artificial one. He struggled with his idea for six years before he was able to put it into practice. J. B. Murphy<sup>7</sup> followed him independently in 1898. Both Forlanini's and Murphy's ideas, however, lay fallow until the beginning of the present century when Brauer<sup>8</sup> took them up again and helped them to a secure footing.

It is to Brauer's rare combination of clinical insight and surgical imagination that we owe the first suggestion for our modern collapse operations. Convinced of the efficacy of collapse of the lung by pneumothorax in unilateral tuberculosis, he sought to extend the benefits of collapse to patients in whom pleural adhesions made pneumothorax impossible. In 1906, he suggested to his surgical colleague Friedrich that he might produce the effect of a pneumothorax by collapsing the whole chest wall. Friedrich<sup>9</sup> carried out the operation by resecting a long piece of all the ribs on one side, i. e., removing the bony frame of almost one half of the chest.

These two procedures, pneumothorax and thoracoplasty, underly our present efforts at a mechanical cure of pulmonary tuberculosis. Both procedures are calculated to compress the affected lung, to immobilize it, to rob it of its respiratory function, and to cause it to shrink. Forlanini's methods for pneumothorax have scarcely been changed in the forty years since their invention. The original Brauer-Friedrich extrapleural thoracoplasty, however, has been abandoned for less severe operations.

4 Emerson. Pneumothorax, Johns Hopkins Hosp. Rep. **11** 1, 1903. Cites Stokes. Diseases of the Chest, 1837. Houghton. Dublin J. M. Sc. **1** 313, 1832. Williams, C. J. B. Diseases of Organs of Respiration, Philadelphia, 1871.

5 Quoted by Sauerbruch. Chirurgie der Brustorgane, Ed. 2, **1**, p. 594.

6 Forlanini. Gaz. d. osp. **3** 537, 585, 601, 609, 617, 625, 641, 657, 665, 689, 705 (Aug., Sept., Oct., Nov.) 1882, Therap. d. Gegenw. **49** 485, 531 (Nov., Dec.) 1908.

7 Murphy. J. A. M. A. **31** 151 (July 17) 1898.

8 Brauer. Beitr. z. klin. d. Tuberk. **12** 49, 1909.

9 Friedrich. Arch. f. klin. Chir. **87** 2, 1908.

Brauer was not the first to have suggested the extrapleural compression of tuberculous cavities. Others—Tuffier,<sup>10</sup> and especially Quincke<sup>11</sup> (we seem to owe most of our advances in lung surgery to the internists)—had tried it before him. It is to Brauer's credit, however, to have recognized the futility of trying to cure pulmonary tuberculosis by applying pressure over a small circumscribed area of lung. He was the first to see the necessity for collapsing the whole diseased lung and to build an operation on this principle.

Quincke (1888) and Spengler<sup>12</sup> had suggested the collapse of tuberculous cavities by resection of part of the upper ribs. Isolated attempts at this local collapse were made from time to time with more or less success until better insight into the effects of pneumothorax made it evident that a total collapse of the lung was necessary for a cure, and that partial operations would meet with but partial success.

The development of our present day procedures for the surgical treatment of pulmonary tuberculosis sheds much light on the rationale of some of them and the futility of others.

The main difficulty and the great interest of this treatment center in the niceties of indication for operation and the choice of procedure. The general indications for surgical collapse are easily formulated. A surgical collapse is indicated for those patients who should have a pneumothorax, but in whom a pneumothorax is impossible. That is an easy formula. It rolls the burden of the choice of patients onto the shoulders of the internist. If he wants to make a pneumothorax and finds he cannot, the surgeon takes his place. However, if the surgeon is to take the responsibility, he should make his own observations, together with the internist, and participate in the internist's conclusions. The surgeon will not regret keeping his patients under observation for several weeks before he makes up his mind. He should, by all means, have the advantage of frequent consultation with his internist during this time.

The indications for pneumothorax and for thoracoplasty are, then, largely the same, namely, a mainly unilateral process with a bad outlook for cure by ordinary conservative means. Physical signs and the roentgen ray, extensive unilateral cavities, repeated hemorrhages, multiple caseous pneumonic foci may often make it apparent from the beginning that the outlook is bad, again, it may take months to recognize that the patient is steadily getting worse in spite of good conservative treatment. It is not necessary that the tuberculosis be entirely unilateral, that one lung be perfect. Probably it never is. It is merely

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10 Tuffier and Martin. *Trait chir de la tuberc pulm*, Paris, Masson et Cie, 1910.

11 Garre and Quincke. *Lungenchirurgie*, Ed 2, Jena, 1912.

12 Spengler. *Verhandl d Naturforscherversammlung* Bremen, 1890.



necessary that the better lung be competent to carry on the work of both, and that it contain no foci that are likely to light up under the additional burden, i e., no large cavities or evidently active areas. Hemorrhages, large amounts of sputum, fever, do not contraindicate operation, but rather strengthen the indications.

A release of the lung by pneumothorax will be most strikingly effective in chronic fibrous phthisis with cavitation. Patients whose lungs have shrunk and drawn with them the mediastinal viscera, who are dyspneic from a kinking or a constriction of the trachea, or who are cyanosed from a displacement of their hearts and great vessels, will be given the greatest relief. They suffer not so much from their tuberculosis, but from deformities of their viscera arising from the process of its cure. The very shrinkage that is going on in the lung shows the cure. Sometimes the tuberculosis may be quite healed and only the deformities provoke symptoms. More often the cure is incomplete. Would the bony thorax but yield and let the lung contract completely, it would heal. It is the rigid chest wall that holds the lung out and keeps the cavities distended. Often one can recognize these patients at first sight. They are the ones who have one side of the chest sunken in, rigid, with no respiratory movement, whose one shoulder has dropped, whose spine is bent toward the affected side.

However, not only this fibrous phthisis, but also the more florid, suppurative and ulcerative form, may be amenable to cure if the affected lung is compressed, kept quiet and allowed to shrink.

Unfavorable for compression are milary tuberculous disseminations.

I have detailed the indications for pneumothorax because, as stated, the same indications hold good for thoracoplastic collapse.

The chronic fibrous phthisics, whose retracted chests give evidence of the natural tendency to a cure, whose course shows the mildness of the disease or the patient's great resistance, are ones likely to be helped by a pneumothorax. But it is in just these patients that a pneumothorax is most frequently impossible. Their chests are shrunk and their mediastina displaced because the lung has everywhere grown fast to them. The same adhesive pleurisy that makes the chest shrink precludes the possibility of getting air into it. Most of our subjects for operation, therefore, will be recruited from this group.

Others, especially those with large superficial cavities in the upper lobe, will come for thoracoplasty after having had a pneumothorax—an incomplete one. Frequently one succeeds in introducing air into the lower part of these patients' chests, one collapses the lower part of the lung, but the upper part, the one containing the cavity, remains tightly fixed to the chest by adhesions.

Others will have open tuberculous empyemas. They have their pneumothorax, their lungs have healed. It remains to close the chest

The contraindications are partly covered by the contraindications to artificial pneumothorax too much involvement of the better lung and miliary tuberculosis To these I might add unwillingness or reluctance of the patient to accept operation The results are not certain enough to force operation on an unwilling patient Unwillingness, however, is infrequent enough More often will one have to reject patients who are unsuitable, even though they plead for operation, than urge the suitable ones to be operated on

Sauerbruch warns us of an idiosyncrasy to morphin or cocain He tells of a woman whom he rejected on this score Another surgeon, ignorant of her peculiarity, operated on her She died on the table

If at all possible, the operations should be done under local anesthesia alone, the addition of a general anesthetic increases the risk greatly It is not the irritation of the lungs by the anesthetic that seems to me so objectionable The chemical irritation of nitrous oxide gas is negligible It is the insensibility of the patient to safeguarding reflexes, his inability to cough, to regulate the depth of his respiration according to his momentary needs and the waste of muscular energy in useless struggling that make general anesthesia dangerous Inspirations or expirations, unregulated by a waking brain and carried out at improper moments, suck and blow tuberculous sputum and pus from one part of the lung to another The lack of a cough reflex stops the patient from coughing material out again once it has been aspirated His useless struggles with his limbs and body and with his respiratory muscles wear out his sorely needed store of energy These are the risks that the surgeon adds whenever he finds it necessary to supplement local anesthetics with gas

Finally, a most important contraindication—no attempt has been made at artificial pneumothorax Artificial pneumothorax is the procedure of choice for collapse of the lung It is easier to do than thoracoplasty, less risky and accomplishes the same result, if it can be carried out It has, moreover, an advantage over thoracoplasty in not being permanent One can stop treatment after the tuberculosis is healed, and if the pneumothorax has not had to be maintained too long the air will gradually be absorbed from the chest and the lung will unfold But a thoracoplasty collapses the chest for good and all

At times, however, the permanence of a thoracoplastic collapse may be no disadvantage At the last meeting of the California State Tuberculosis Association, I learned from members of large experience that insufflations of gas, once they have been begun, must be continued over very long periods This, I think, is worth considering in weighing the desirability of a permanent collapse Were I a tuberculous patient whom a pneumothorax had restored to well being but who relapsed as soon as the air in my chest was absorbed, were I a patient wedded—or

chained, if you like—to a doctor's doorstep by the need of a series of refillings to which I could see no end, it seems to me that I should be delighted at the prospect of an operation which would release me from medical surveillance. When clinical experience, therefore, shows the probable necessity for a very long continuance of pneumothorax, when after a year or more even the very gradual expansion of a previously active tuberculous lung is followed by renewed activity, it seems to me worth while to consider supplementing or supplanting the pneumothorax by a thoracoplasty. And all the more because previous gas compression of a lung makes surgical compression both technically easier and less dangerous.

One never can tell, in spite of roentgenoscopy and all manner of diagnostic attempts to show pleural adhesions, whether the lung is bound down tight or not, and whether a pneumothorax is possible or not, unless one tries it. Thoracoplasty, therefore, should never be done before pneumothorax has been tried, and has failed or proved insufficient.

The surgeon will usually place more reliance on the internist's opinion and diagnostic findings than on his own. And unless he is an uncommonly good diagnostician, he will be afraid to proceed alone without the help of a competent internist. But final judgment for or against operation, what, and how much to do, rests with the surgeon.

To know his own mind he should have the patient under observation for a reasonable time, at least a week or two, before operating. The surgeon's viewpoint is different from that of the medical man. No matter how accurate clinical observation has been, the surgeon should see and judge for himself. He will learn a great deal about tuberculosis, things which he never knew, or had forgotten. It is surprising how often simple observations, which are far more important surgically than the judgment of râles or resonance, are overlooked in patients with detailed charts and records. The shape and movements of the thorax especially which part is retracted, which part moves and which stands still, inspiratory retraction in the intercostal spaces, the position of the trachea in the sternal notch, are often overlooked. The respiratory capacity of the lungs and the daily quantity of sputum should be recorded. All these factors are of considerable importance.

It is often as difficult to decide on the type of operation as it is to know whether to operate at all. There are several methods for total collapse, and several for partial collapse. Sauerbruch and others of experience seem agreed that partial collapse is to be used only in conjunction with the methods for total collapse, *i. e.*, together with artificial pneumothorax, or after a total thoracoplasty has failed sufficiently to compress circumscribed areas of lung. Partial collapse of the upper lung alone, as a primary procedure, is dangerous and rarely leads to a cure. Disastrous aspiration of tuberculous pus into the lower parts

of the lung during operation on cavities in the apex has shown that the lower parts should always be collapsed first. Flooding the lower part of the lung with pus is the chief cause of postoperative mortality. This caution applies to nontuberculous abscesses of the upper lung as well.

There are two procedures for total collapse of the chest. The first, the Brauer-Friedrich operation, consists in the removal of large sections of the second to the tenth ribs. Under general anesthesia, a long fishhook shaped incision is made between the scapula and the spine and carried forward toward the nipple. The scapula and soft parts are pushed up from the chest and long pieces of rib are removed rapidly. This divests half of the chest of its bony support. It is evident that the procedure entails considerable shock and has alarming consequences. The patients breathe almost as though they had a wide open pneumothorax. The unresistant chest wall flaps back and forth with each respiration. For the first few days the dyspnea is alarming. It is necessary to steady the chest by various devices: turning the patients on the operated side, strapping the chest with adhesive, firm bandaging, etc. Unless one gives the chest some hold, the patients merely gasp ineffectually for breath. The bellows which move the lungs are too flabby to pump air in and out. If the patients survive the first few days, they gradually accustom themselves to the new type of breathing. Many of them, however, succumb to the intense air hunger. The operation carries with it too high a mortality to be of wide use. It may, however, still be indicated in patients in whom a thick or resistant pleura, or a thick and unyielding mediastinum, separates the chest into two distinct compartments, so that the one will be stiff enough to carry on the work of respiration even though the other be totally out of commission. Its sphere will probably be limited to the after-treatment and collapse of open tuberculous empyemas. In these cases it may be carried out after the manner of a Schede thoracoplasty with considerable prospect of success.

Sauerbruch's procedure has many advantages over Friedrich's and has superseded it. Sauerbruch collapses the chest by resecting smaller portions of all the ribs through a paravertebral incision. His resection is carried out close to the spine, at the costal angle. His procedure is much less mutilating, it diminishes the thoracic volume very nearly, if not quite, as much as Friedrich's operation, and it has the great advantage of producing collapse without robbing the chest of its rigidity—of its bony support. It is necessary, in order to get a good collapse, that the ribs be resected close to the spine. When this is done, the chest is narrowed not only in the transverse, but also in the sagittal diameter. The ribs not only cave in, but their sternal ends drop down nearer the backbone. The vertical diameter of the chest is lengthened. The chest

becomes narrower both fore and aft and sidewise, but it also becomes longer. The ribs run almost vertically instead of horizontally, the intercostal spaces are much narrowed, especially toward the back. The reasons are clear when one thinks of the way in which the ribs are suspended. Their fixation points lie at the two costovertebral joints, the joint between the head of the rib and the vertebral body, and the joint between the tubercle of the rib and the transverse tuberosity. These two joints determine the position of the ribs and hold them firmly out from the spine. The sternal end of the rib is flexible. One can cut the ribs off from one side of the sternum entirely and they will still maintain their position in a transverse plane fairly stiffly. If, however, one cuts the connection between the ribs and the spine on one

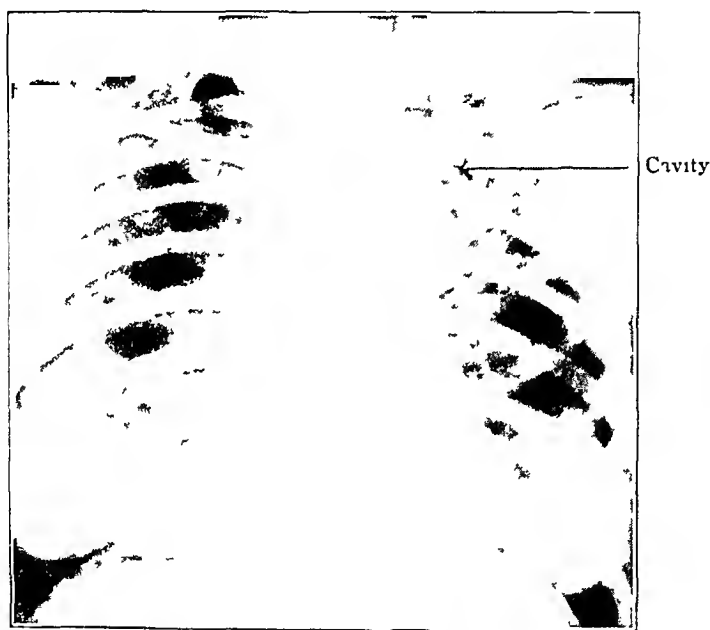


Fig 1—Before pneumothorax, showing large cavity of right upper lobe

side, that side of the chest becomes freely movable and drops down by its own weight, the weight of the viscera suspended from it, and the pull of the abdominal muscles. This drop and the vertical narrowing may be seen by comparing Figures 9 and 10, and Figures 17, 18 and 20.

The amount of collapse produced by the resection of only a few centimeters of the posterior part of the ribs is astonishing. Compression occurs, as stated, in two directions—transverse and sagittal. The diminution in the sagittal diameter becomes apparent immediately the lower two or three ribs have been cut across. As we continue our resection upward, the collapse increases before our eyes. The chest wall falls in toward the midline more and more as we proceed. The



Fig 2—After pneumothorax, showing cavity still uncollapsed, its walls held distended by adhesions A-Adhesions

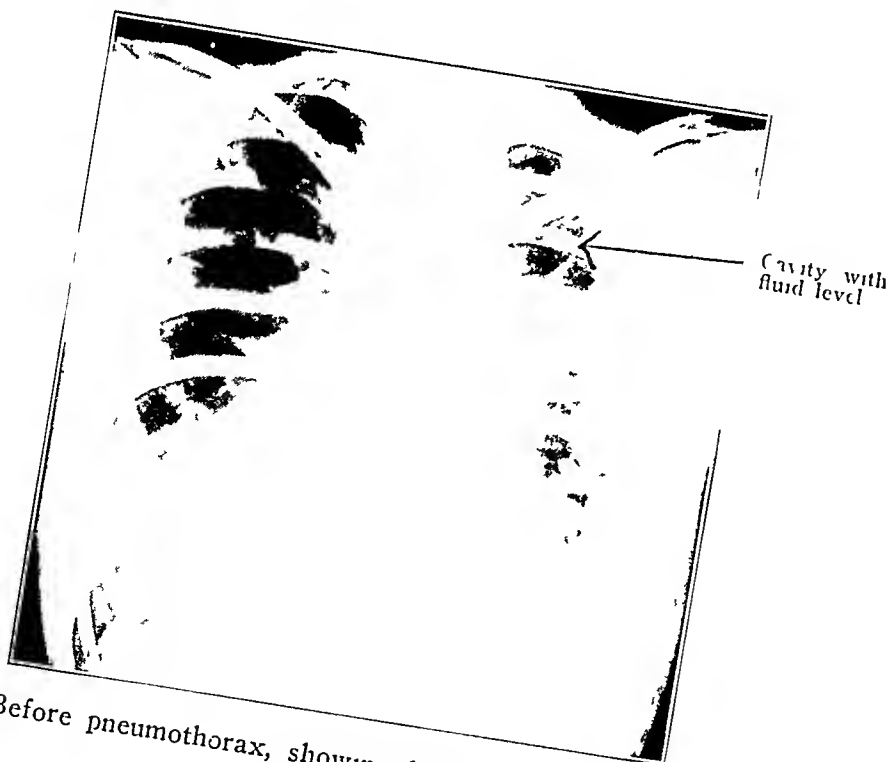


Fig 3—Before pneumothorax, showing large cavity with fluid level

diminution in the other direction, the transverse decrease, which is caused largely by the dropping down of the ribs, does not become apparent until the two uppermost ribs are cut, especially the top one, which is the main support from which the chest is suspended. The collapse is striking as soon as the first rib is severed. The whole chest wall drops down suddenly, like a tent whose pole has been taken from under it. This drop does not occur until the first rib is cut through, but after that the whole chest drops downward several inches, one rib following the other like a series of card-houses. The downward shift usually covers from one and one-half to two intercostal spaces so that the sternal end of the first rib lies opposite the vertebral stump of the third rib, or even lower.

Sauerbruch's operation is by far the better procedure for total collapse. It is much less shocking than the Brauer-Friedrich's thoracoplasty. It can be done under local anesthesia, a very great advantage. It can be done in several stages. We can stop our resections at any time if the patient becomes dyspneic. There are no alarming after-effects. It does not upset the whole respiratory mechanism by robbing half of the chest of its bony framework.

It is really easier than it might seem. In the beginning I planned to do the operation in several stages. But I found it necessary to stop short only once in the five patients. In three cases I was able to resect pieces of all of the ribs, from the first to the twelfth, at one sitting, in one case, the first of the series, I left the first rib, ignoring its importance, and had to remove it at a second sitting.

The patients are not visibly deformed. No one would notice the deformity when they are clothed.

Following the ideas of Webb, the patients are laid on the operated side after operation so that the weight of the body may further the collapse and keep the affected side quiet. They are given morphin or codem, and are turned twice a day so that they may cough out the accumulated secretions. If possible, the posterior edge of the scapula is laid in front of the vertebral stumps of the ribs so that it may push the chest still further inward. The patients are kept in bed about eight weeks.

The chest is collapsed, as stated, both in the transverse and the sagittal diameter. There are no respiratory movements, except in the upper anterior part of the chest. The sternal ends of the first two or three ribs move. They are carried along by the sternum, I think, with the respiratory movements of the unoperated side. Below the scapula, where the resected ribs are most movable, the chest wall often moves paradoxically with respiration—that is, it is retracted on inspiration and moves out from its inspiratory position when the patient breathes out.

The collapsed side is dull to percussion, but on auscultation all sorts of sounds are heard loud bronchial breathing and various squeaks, rubs and râles. All observers are agreed that it is very difficult to judge of the meaning of these physical signs. The bronchial breathing probably comes from the air in the bronchi causing a whistle to be transmitted loudly through the shrunken and solid lung. The squeaks and râles are partly pleuritic and partly produced in the atelectatic alveoli.

The mediastinum and heart, which before operation are often pulled far over toward the affected side, frequently return to the midline after operation.

The respiratory rate has not increased after operation.

We have had no untoward results. It is too early to speak of cures, but all of our five patients have improved. None has had elevation of temperature. The sputum has diminished in all of them. One patient has no sputum at all, two patients expectorate about 4 c c a day. Two still bring up from 15 to 30 c c a day. Two of those with sputum show no tubercle bacilli on repeated examinations. All of them have gained or held their weight, look well and are free from pain, their disease has been arrested or has diminished in extent.

We have been fortunate enough to avoid an aggravation on the better, unoperated side. Indeed, in some of the cases not only the operated but the unoperated side has been improved. The improvement was noticed clinically, and Dr. Bryan also called attention to the marked differences in the roentgenograms. We have been fortunate, but others have noted the same thing. They have tried to explain the improvement in various ways. They have said that the lung was like the kidney in that the less affected one improved as its neighbor improved, that the appetite and general resistance were benefited by the abolition of cavities and expectoration.

One can go farther than this. Stivelmann, Hennell and Golembe,<sup>13</sup> and Barlow and Kramer<sup>14</sup> seem agreed that there may be anatomic grounds for the bilateral improvement. It seems to me that we are far too prone to look on the two halves of the chest as two separate and independent compartments. They are not. Whatever changes the pressure on one side will change the pressure on the other. The mediastinum is not a sheet iron wall. It is an exceedingly thin and yielding membrane. One can see it change its position after operative collapse of the chest. The measurements of Simon<sup>15</sup> show that pneumothorax lowers the tension not only in the collapsed but in the contralateral half of the chest, and that the decrease is about equal on

13 Stivelmann, Hennell and Golembe. *Am Rev Tuberc* 6 95, 1922

14 Barlow and Kramer. *Am Rev Tuberc* 6 75, 1922

15 Simon. *Tr Nat Tuberc Assn*, Seventeenth Meeting, 1921, p. 402



both sides Collapse, therefore, compresses not only the collapsed side but the other side as well, so that not only the affected lung, but also the unaffected lung, should reap some of its benefits Releasing the shrunk side from the tug of its pleura should help the emphysema and distortion of the less affected lung, and put it in a better position to use its powers of shrinkage where they are needed, i e, over its tuberculous areas

In discussing the various operative procedures we stated that the total collapse of Sauerbruch was the operation of choice, that partial collapse was dangerous, and that we had been able in every case but one to resect pieces from all twelve ribs in one sitting This is true, but a single resection is sometimes insufficient Some cavities are not obliterated by it The fault lies not with the operation, but with the cavity One can always decrease the volume of the thorax sufficiently to relieve the lung of all tension Some cavities, however, are so stiff-walled that they will not collapse even when there is no tension on them at all These stiff-walled cavities have to be pushed in if they are to be obliterated Their walls will never fall in by themselves Here partial resection and partial compression enter the field

There are various methods the columnar resection of Wilms,<sup>16</sup> who removes a piece of rib both anteriorly and posteriorly, intrapleural apicolysis, where the hand is introduced into the pleural cavity and adhesions broken down extrapleural apicolysis, where the pleura of the upper thorax is loosened from the chest wall together with the underlying adherent lung, and the methods of Tuffier<sup>10</sup> and of Baer,<sup>17</sup> who compress the lung with a free graft of fat or with soft paraffin, and of Archibald<sup>18</sup> who places a tampon of muscle over the cavity Partial collapse is particularly indicated when an artificial pneumothorax succeeds in compressing the lower part of the lung, but where the apex and its cavities are held stretched out to the chest wall by firm pleural deposits When a partial pneumothorax is possible, its combination with partial thoracoplasty is an ideal procedure A partial pneumothorax compresses the lower part of the lung, after this a thoracoplasty may compress the upper part with impunity There is no danger of aspirating material from an upper cavity into the lower lung after the lower lung has been compressed by a pneumothorax

I have had to supplement Sauerbruch's thoracoplasty with an operation on the apex twice The first patient had an enormous cavity with sputum up to almost a pint a day Beneath the cavity she had a pyopneumothorax which Drs Whitney and Richter, who were kind enough to send her to me, had aspirated and washed out at intervals

16 Wilms *Munchen med Wchnschr* 60 449, 1913 61 865, 1914

17 Baer, G *Ztschr f Tuberk* 23 209 1914

18 Archibald *Tr Am Surg Assn* 1922

A Sauerbruch resection obliterated the pyopneumothorax and lessened the diameter of the cavity by about one half, but did not obliterate it. The sputum dropped at first to about 50 c c a day, then rose again to about 100 c c. Two months after the first operation, I resected an inch of the clavicle and considerable pieces of the upper four ribs through an anterior incision. The sputum diminished to about 30 c c, the cavity is much smaller but it is not yet collapsed. Of late her sputum has again increased and a cold abscess has broken through the chest from her old empyema. A third operation will probably be necessary.

A second patient operated on in two stages by the Sauerbruch procedure also retained a considerable cavity at her apex. At a third operation I removed an inch of clavicle and practically all that remained of the first and second ribs, as well as three and a quarter inches of the third rib.

#### REPORT OF CASES

**CASE 1**—Mrs M. M., a housewife, aged 29, was referred by Dr Philip King Brown to the San Francisco Hospital, March 1, 1921. She was discharged, Dec 22, 1921. She has two children.

**History**—She had measles in March, 1920. Following this she complained of increasing weakness, cough and fever. For the past year she has had afternoon temperature of 99 and 100 F. She expectorates 25 or 30 c c of sputum a day. At times it is blood streaked. Various attempts at pneumothorax have failed.

**Examination**—March 29, 1921, Dr Clark examined her and found her to be undernourished. The thorax was long, flat and broad. The left shoulder was lower than the right, and the respiratory movement of the chest was restricted on both sides, decidedly more on the left side than on the right. The whole left side was dull, it was flat down to the seventh dorsal vertebra and less dull below. It was dull in the left axilla. On the right side there was dulness above the clavicle and posteriorly down to the second dorsal vertebra. The right side of the diaphragm moved fairly well, the left side moved very little. There were râles in the upper left chest on coughing, with amphoric breathing. There were also râles below the left clavicle. There were râles over the right clavicle and over the right fifth rib. The heart was displaced to the left.

TABLE 1—SUMMARY OF DATA IN CASE 1

	Tempera- ture, F	Pulse	Respira- tion	Sputum, C c	Weight, Pounds
Before operation	98.6-100-102	80-110	20-35	25-30	112
Postoperative abscess, April 14-20	98-101-102	80-140	30-45	?	?
April 26 to July 1	98-99.5	90-120	30-40	6	104
July 1 to August 1	98-99	90-120	30	0-5	?
August 1 to September 1	98-99	80-100	25-30	10	104-114
Second operation September 19-25	98.6-102	90-120	25-40	10	
September 25 to December 22	97.8-98.6	85-100	22-25	5-10	?
Discharged, April 13, 1922	98-98.8			0	134

Sputum March 2, 1921, Tb + Aug 26, 1921, Tb +, Oct 28, 1921, negative

Urine negative

Blood Hemoglobin, 80 per cent, red blood cells 5,000,000, white blood cells, 8,850 to 11,850, polymorphonuclears, 62 to 72 per cent, small lymphocytes, 38 to 25 per cent, Wassermann negative

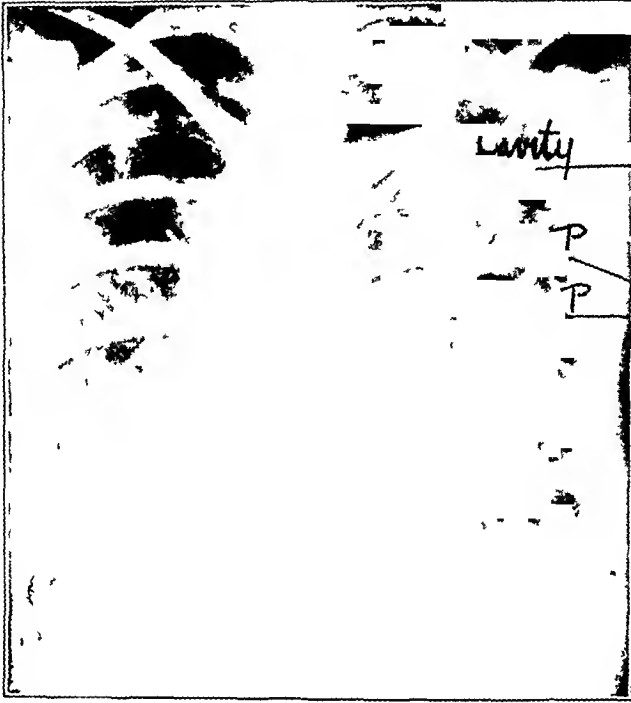


Fig 4—After pneumothorax, showing cavity held distended by adhesions, still uncollapsed P-Pneumothorax

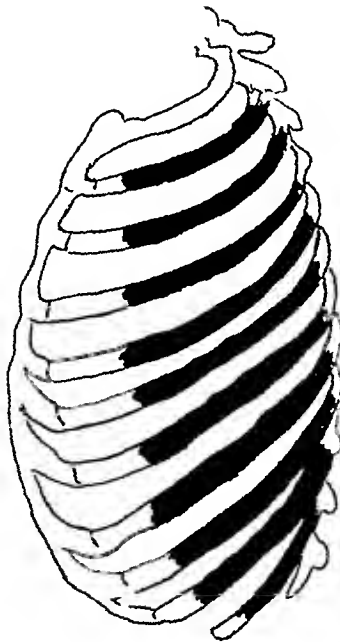


Fig 5 Amount of ribs resected in Friedrich operation

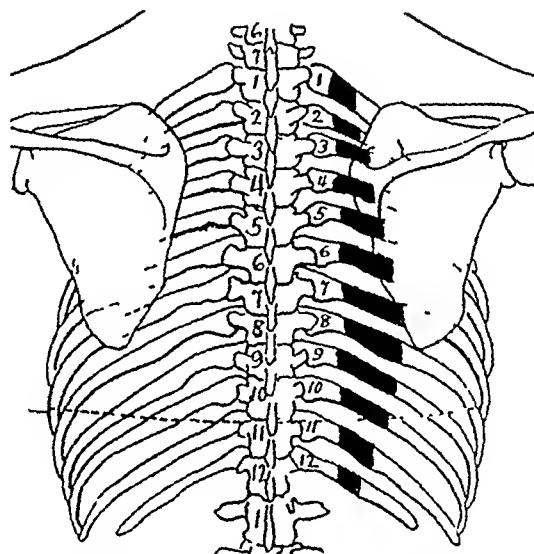


Fig 6—Amount of ribs resected in Sauerbruch operation

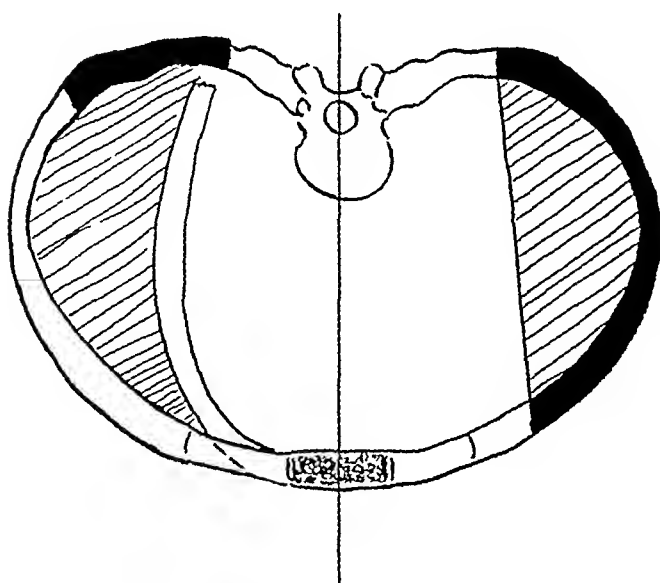


Fig 7—Diagram of cross-section of chest Friedrich's resection on the right side, Sauerbruch's on the left, amount of rib removed shaded black Although the amount of rib resected in the Sauerbruch operation is much less, the collapse is almost, if not quite, as great as after the Friedrich operation



Fig 8 (Case 1) —Before operation Large cavity left apex Infiltrate below  
Considerable mottling right side

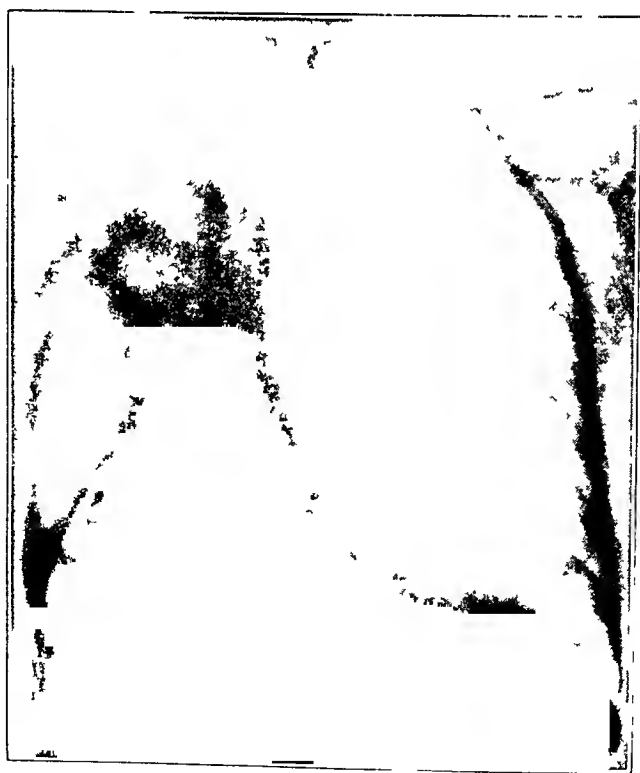


Fig 9 (Case 1) —Five months after first operation First rib not resected  
Collapse incomplete No sinking downward of left chest Cavity of left apex is  
smaller, but is not yet collapsed Scoliosis to left and compensatory dilatation  
of right lung

Roentgen-ray examination, March 21, 1921, disclosed a cavity in the upper left side of the chest and an infiltration on the left side

*Diagnosis*—Cavities in left side Thick pleura left base Thick pleura right apex Active tuberculosis upper and middle lobe, right

*Treatment*—FIRST OPERATION April 14, 1921, under satisfactory local anesthesia from the second to the eleventh ribs were resected according to Sauerbruch's method The resected pieces measured as follows Second rib, 3.75 cm, third rib, 3.75 cm, fourth rib, 3.25 cm, fifth rib, 3.25 cm, sixth rib, 3.5 cm, seventh rib, 2.75 cm, eighth rib, 2.6 cm, ninth rib, 2.25 cm, tenth rib, 1.75 cm, eleventh rib, 0.5 cm The pleura was opened and cobweb adhesions were seen No pneumothorax resulted The lung was grasped with a hemostat and pulled about This was done to find the cause of the pain in adhesive pleurisy The patient, however, felt no pain during this maneuver After cutting the second rib, the chest as a whole dropped back toward the spine The medial edge of the scapula was placed under the stumps of the ribs



Fig 10 (Case 1)—Four and one-half months after second operation Cured First rib resected, additional pieces removed from second and third ribs Left chest has sunk down so that peripheral stump of first rib lies opposite central stump of third rib Peripheral stumps of first and second ribs united by bony callus Cavity completely collapsed Note the difference between Figures 9 and 10 (before and after resection of the first rib) After resecting the first rib the upper chest is much narrower and the cavity completely collapsed

*Course*—April 15, the heart had returned to its normal position the apex was in the left nipple line and the right border was at the right sternal edge

April 25, some pus containing staphylococci appeared in the wound It contained no tubercle bacilli (guinea-pig inoculation)

August 23 Up to ten days ago the patient had no sputum She now has 1 cc per day After "catching a cold" she had more sputum and cough

September 16 Roentgen-Ray Examination Medial part of left diaphragm moves about one-half inch There is a small area of mottling at the base of the right upper lobe with interlobular thickening

September 17 The cavity at the left apex still remains

SECOND OPERATION September 29, a second operation was undertaken Under satisfactory anesthesia the first, second and third ribs were resected The second and third were joined by callus The resected pieces measured First rib 3 cm second rib, 5 cm, third rib 2.5 cm After resection the apex collapsed Part of it was hard, but the top of the apex was soft and blew in and out on respiration as though it contained a thin walled cavity

September 22 The patient was discharged to convalescence at Arequipa She felt well, was gaining weight, and had no sputum

April 13, 1922, she was finally discharged She has gained 24 pounds since her first admission Her color is good, she looks robust and sturdy She is now doing housework, has no cough, no sputum, and may be considered cured

CASE 2—Miss E W, a nurse, aged 28, was referred by Dr Philip King Brown to the San Francisco Hospital where she stayed from March 29 to Aug 6, 1921

*History*—One brother died of tuberculosis At the age of 3 she had pneumonia and at 14 she had "grippe" She was in bed and was kept out of school for six months, and did not feel well during this time Six years ago she had an hemoptysis of a few ounces This recurred several times, the last time on Christmas day, 1920 For the last six years she has had afternoon rise in temperature at times, in February, 1921 her temperature was 100 and 101 F Three years ago she had a pleurisy which lasted off and on for two years For the last one and one-half years she has had to sit up in order to breathe She had four attacks of dyspnea, each lasting three weeks, and at this time she had fluid in her chest She was at Arequipa twenty-two months with daily sputum measuring from 25 to 50 cc For the past eleven months she has been at the Marin County Infirmary and has had from 50 to 100 cc of sputum a day Eleven attempts at pneumothorax were made at Arequipa but were only partially effective, as follows

1919	Feb	8	75	c c	air		April	5,	no	air
	Feb	15	75	c c	air		April	8,	65	c c
	Feb	22,	190	c c	air		Dec	27,	100	c c
	March	1	225	c c	air					
	March	8	350	c c	air	1920	Jan	3,	65	c c
	March	15	225	c c	air		Jan	10	100	c c
	March	22	140	c c	air		Jan	24,	225	c c
March	29,	no	air	Jan	31,		50	c c		

While at Arequipa she gained 33 pounds in weight (137-170 pounds) but had frequent hemorrhages Lying on her right side makes her cough and bring up more sputum She sleeps on her back or on her left side

*Examination*—May 3 1921, Dr Clark examined her and found a well nourished girl with a sunken right chest The whole right side was dull, except just under the clavicle There was amphoric breathing at the right apex with bronchial breathing at the right base and right hilus There were bubbling râles on the right side The left side was hyperresonant and there were moist râles at the left base (communicated from right?) There were no râles over the left upper chest

Dr Eloesser's examination reads Right side moves, but less than the left The right clavicle does not rise as much as the left and the right chest excursion is less than the left The upper right quadrant, under the pectorals, rises well

*Diagnosis*—Chronic tuberculosis Cavity of the right lung

*Treatment*—Before operation the sputum measured from 50 to 100 cc For the first four weeks after operation it averaged 20 cc a day, then 15 cc

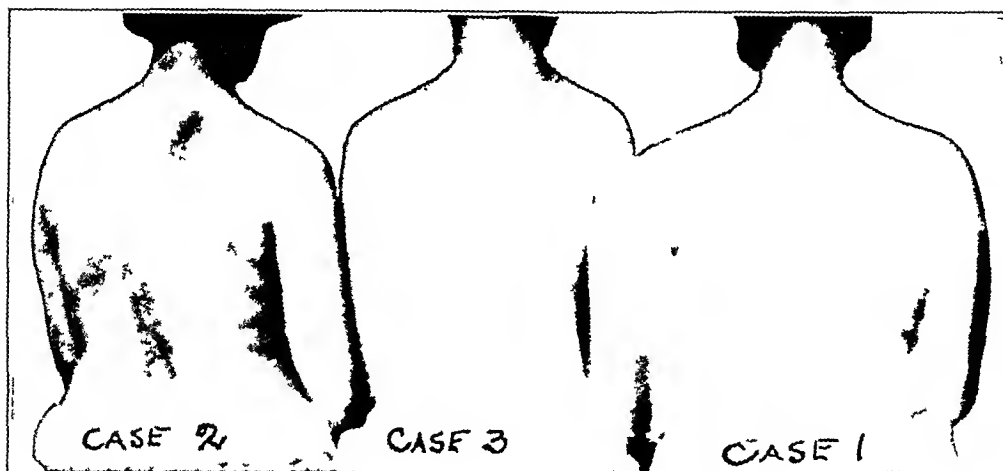


Fig 11—Case 1 After operation Collapse of left side Gain in weight  
 Case 2 After operation Collapse of right chest Marked scoliosis Case 3  
 After operation Collapse of right chest Marked scoliosis



Fig 12 (Case 2)—Before operation Before pneumothorax Pleurisy with  
 effusion right base



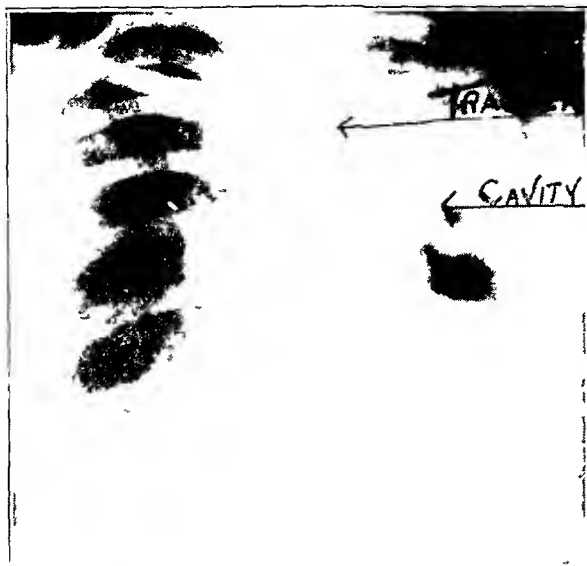


Fig 13 (Case 2) —Before operation Effusion absorbed Large cavity middle right lobe Trachea drawn to right



Fig 14 (Case 2) —Fifteen days after operation Distal end of first rib in first interspace Collapse incomplete Considerable gap between ends of resected ribs Trachea is drawn to right No cavity seen



Fig 15 (Case 2)—Seven weeks after operation Collapse much more marked, especially around middle and lower parts right chest Distal end of first rib in first interspace Heart has moved to the left Trachea is drawn to right



Fig 16 (Case 2)—Ten months after operation Peripheral end of first rib in first intercostal space No further signs of cavity Good collapse, especially of upper part of chest Trachea is drawn to the right The usual scoliosis is absent This figure is a combination of two films the one overexposed to show the collapsed side, the other with a normal exposure for the good side

May 4, 1921, under satisfactory local anesthesia, the ribs were resected. The resected pieces measured, First rib, 15 cm, second rib, 27 cm, third rib, 45 cm, fourth rib, 73 cm, fifth rib, 67.5 cm, sixth rib, 75 cm, seventh rib, 8 cm, eighth rib, 8 cm, ninth rib, 8 cm, tenth rib, 62 cm, eleventh rib, 62 cm, twelfth rib, 45 cm. The collapse of the chest began to be evident after removing the ninth rib. After removing the fourth, fifth and sixth ribs, those overlying the cavity, the patient began to expectorate large quantities of sputum. The collapse amounted to from 3 to 4 inches in the transverse diameter.

*Course*—Miss W made a smooth convalescence and was discharged from the San Francisco Hospital, Aug 7, 1921, with an average of 15 cc of sputum a day and normal temperature.

She was readmitted to Arequipa for convalescence, August 15, and while there had sputum averaging from 10 to 12 cc a day. Between Dec 5, 1921, and May 1, 1922, during which time she worked in the laboratory, she made twelve careful examinations of her own sputum and found no tubercle bacilli. She was up twelve hours a day.

May 21, 1922, she stated that since November, 1921, when she had a cold, she had been sleeping on the good side because she found it easier to breathe and because she coughed when she lay on her bad side. The right side showed a marked inspiratory retraction (paradoxical breathing) under the scapula. On coughing or making a forced expiration, the right side bulged out. There were amphoric breathing and moist râles in the right axilla.

TABLE 2—SUMMARY OF DATA IN CASE 2

	Temperature F	Pulse	Respiration	Sputum, Cc	Weight, Pounds
Before	98-100	70-100	20-25	50-100	172
After	98-99	80-100	20-25	20>15	163
Urine negative					
Blood Hemoglobin 80 per cent, red blood cells 4,100,000					
Sputum May 1, positive, June 23, negative, August 2, 3, and 4, negative for Tb					

Except for the 10 cc of watery sputum, without tubercle bacilli, which she brings up every day, the patient is cured. She is up every day, feels well, and is going East next week.

Twelve additional examinations, made from Dec 5, 1921, to May 1, 1922, were negative. Spirometer readings notes lost.

**CASE 3**—Miss T T student aged 25, was referred by Dr Philip King Brown to the San Francisco Hospital. She stayed from July 8, to Oct 12, 1921.

*History*—Her illness began after an attack of influenza, in December, 1919. In June, 1920, she had two hemorrhages. She entered Arequipa in September, 1920, but in spite of careful conservative treatment lost ground steadily. She is nervous, her heart is irritable, and there is possibly an element of hyperthyroidism. On admission to Arequipa her temperature was 100.4 F, it rapidly receded to 98 and 99 F, and rarely reached 100 F. Three attempts at pneumothorax were unsuccessful, at a fourth a pleural pocket was injected with 75 cc of air.

*Examination*—She was admitted to the San Francisco Hospital, July 8, 1921. The right side of the chest was contracted and scarcely moved on respiration. There was a diffuse fibrous thickening of the right lung with at least three large cavities. There were diffuse bubbling râles all over the right side. There was an audible wheezing stridor. The right diaphragm was adherent to the lung and moved only very slightly. The sputum measured 40 cc. Spirometric measurements were not made.

*Treatment*—**FIRST OPERATION** July 19, 1921, thoracoplasty was done under satisfactory local anesthesia the fourth to twelfth ribs being resected. They measured Fourth rib 14.7 cm, fifth rib 13.3 cm, sixth rib, 12.5 cm, seventh



Fig 17 (Case 3) —Roentgenogram made before operation Three large cavities without fluid level in right upper and middle lobes Increased peribronchial thickening in left lung Right side is shrunk Trachea is pulled to the right No scoliosis

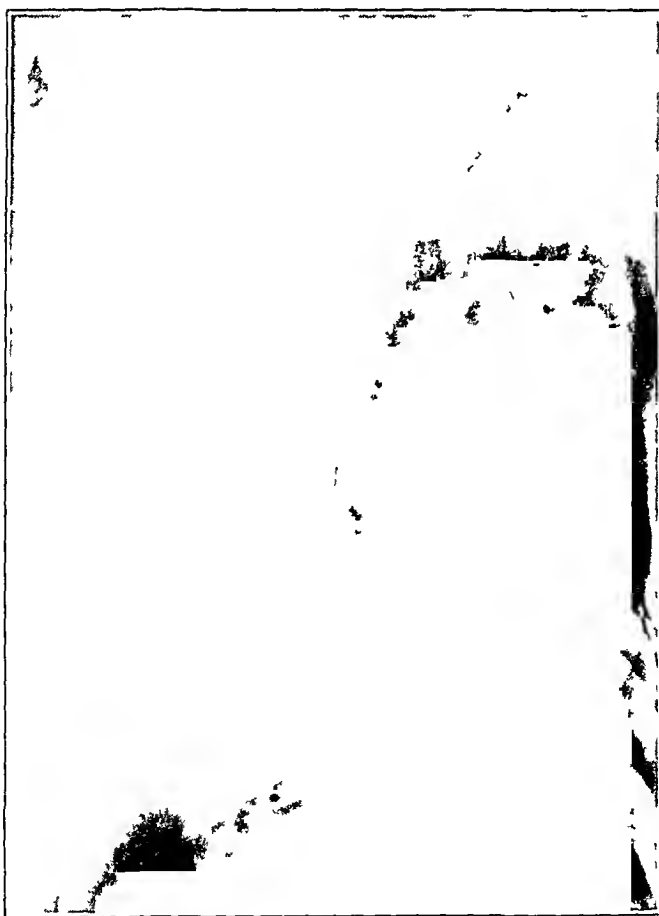


Fig 18 (Case 3) —Three weeks after first operation Three upper ribs remain Upper chest uncollapsed Trachea and heart still pulled to right Slight dextroconvex dorsal scoliosis This is seen to increase in the following figures

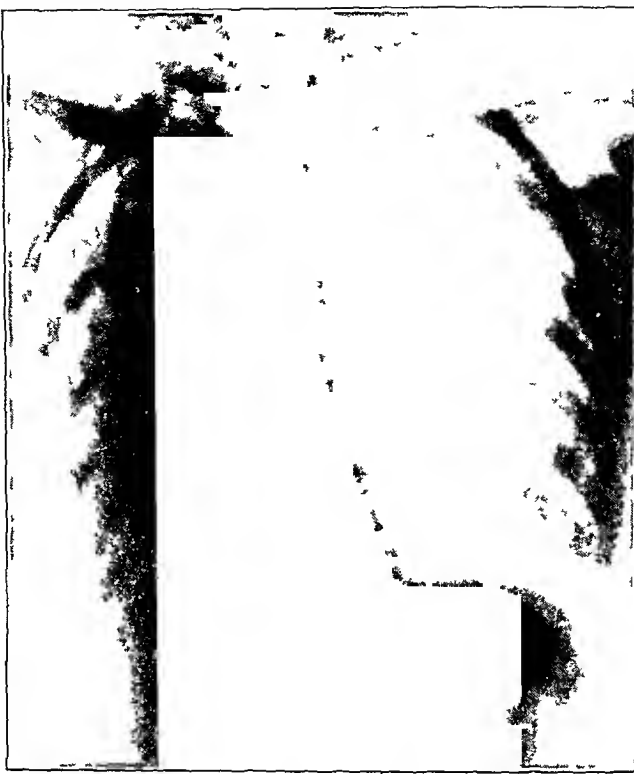


Fig 19 (Case 3)—Six weeks after second operation All ribs resected  
Distal piece of first rib is opposite central stump of second



Fig 20 (Case 3)—Five and one-half months after second operation Extensive regeneration of resected ribs Distal pieces of first and second ribs lie in second intercostal space and are welded to the central stump of the second rib by bony union Bony union between the central stumps of the first and second ribs Large cavities remain at the right apex and in the right middle lobe

rib, 14.1 cm, eighth rib, 11.7 cm, ninth rib, 11.2 cm, tenth rib, 11.5 cm, eleventh rib, 8.8 cm, twelfth rib, 5 cm. After the fourth rib had been reached the patient became dyspneic and it seemed safer to stop the operation.

*Course*—The dyspnea continued to distress the patient for several days, but by the end of a week she was breathing easily. The sputum averaged 20 cc a day.

**SECOND OPERATION** Aug 31, 1921, the vital capacity measured 1,550 cc. On this date the remaining three upper ribs were resected as follows: First rib, 2 cm, second rib, 4 cm, third rib 6.9 cm. The patient stood the second operation well. Breathing was not labored. The following week she suffered considerably from dyspnea.

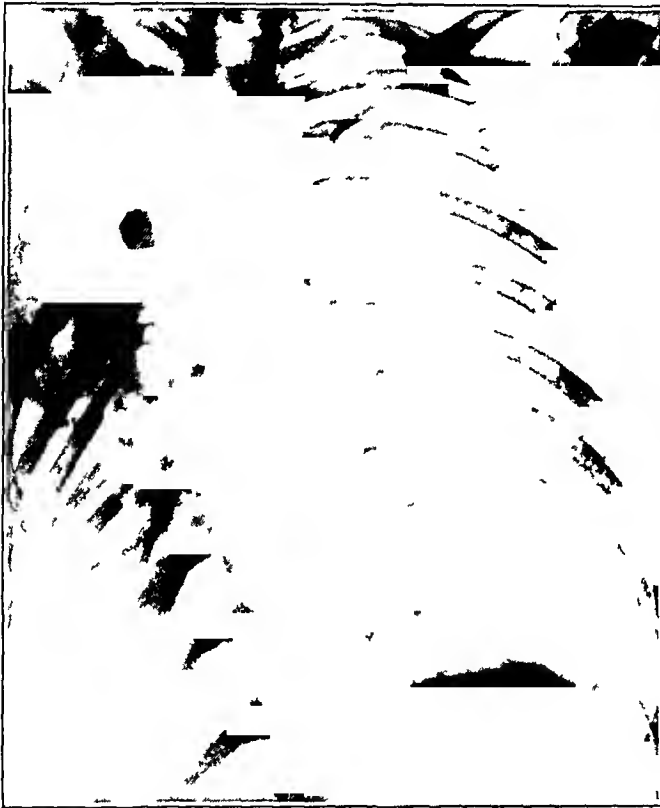


Fig 21 (Case 3)—Six weeks after third operation. The clavicle has been resected and has united. Only the central ends of the first and second ribs are visible, their distal ends seem to have been removed completely. Extensive regeneration of resected ribs. The cavities are much smaller, but still plainly visible. Trachea seems to lie in midline. Marked dextrodorsal sinistrolumbar convex scoliosis, this has developed in the eight months intervening since Figure 17 was made.

*Course*—Oct 7, 1921, the notes read: Left shoulder is lower than right. Sinistrolumbar convex, dextrodorsal convex scoliosis. Inspiratory retraction below right scapula. Heart beat visible and palpable on the right side, mid-axillary line, fifth intercostal space. Lower part of chest does not move on inspiration. Upper part is lifted just a little. Dulness on right, except just over clavicle. Amphoric breathing and egophony here, and at the lower angle of the scapula. The rest of the right side is silent, except for a faint pleural rub. The left side shows only a few isolated râles and a pleural rub.

Oct 12, 1921, the vital capacity measured 1,400 cc (a reduction of 150 cc from the reading before the second operation) The sputum averaged 175 cc a day and September 21 still contained tubercle bacilli

She was discharged to Arequipa Oct 13, 1921 During the first half of November she brought up from 15 to 20 cc of sputum per day In the middle of November, after a corvza, the sputum increased to 25 and 40 cc The cavity was still visible under the fluoroscope

THIRD OPERATION Jan 22, 1922, Dr Brown sent her to the St Francis Hospital for a third operation This was performed Jan 31, 1922, about one inch of the left clavicle and practically all that remained of the first, second and third ribs being resected under satisfactory local anesthesia The resected bones measured as follows Clavicle, 25 cm , first rib, 37 cm , second rib, 8 cm , third rib, 9.4 cm

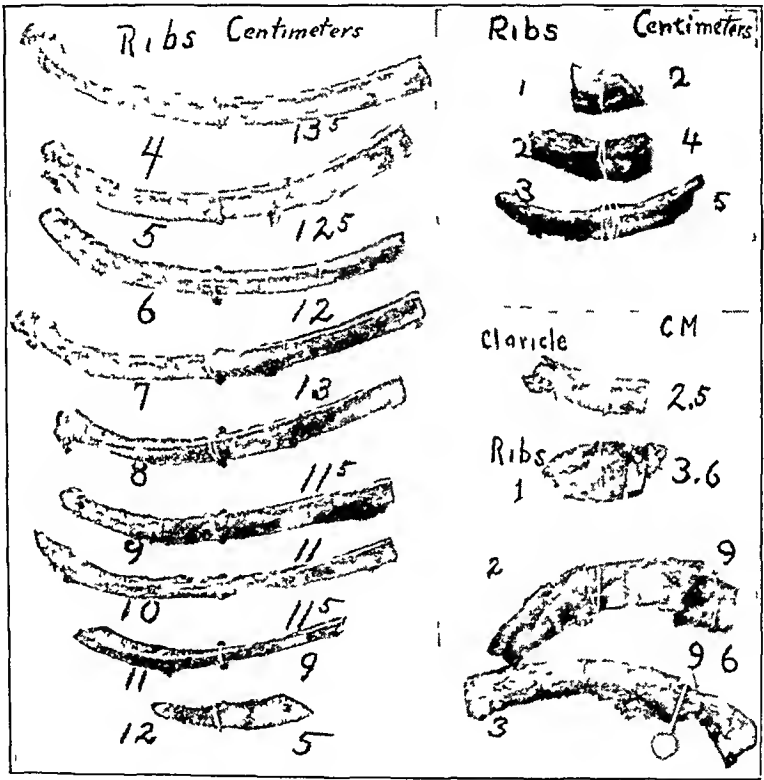


Fig 22 (Case 3) —Ribs resected at first, second and third operations

Course—The patient suffered considerably from dyspnea for the first few weeks following operation, but made an otherwise uneventful recovery and was discharged to Arequipa, March 16, 1922 Her sputum measured from 3 to 25 cc per day, averaging about 15 cc Her temperature was normal

TABLE 3—SUMMARY OF DATA IN CASE 3

	Temper- ture F	Pulse	Respira- tion	Sputum, Cc	Weight, Pounds
Before operation	98-99.5	80-100	20-30	40	128
July 18 to Aug 20 1921	98-99.5	100	20	20	124½
September 1 to Oct 13 1921	98-99.5	100±—	20-30	17.5	123<127
Sputum Tb positive Sept 21 1921 and June 20 1922					

Examination, May 21, 1922, showed the right side standing still, except in the very upper part. There was an inspiratory retraction of the soft parts under the right scapula. There were no bubbling râles anywhere. There was a fine pleural rub at the left base. Her breathing was still wheezy. She was slowly gaining weight. The outcome seems doubtful.

CASE 4—Miss K. O., a seamstress, aged 45, was referred by Drs. C. M. Richter and J. L. Whitney, and entered the San Francisco Hospital, July 30, 1921.

*History*—Tuberculosis was discovered ten years ago. About 1915 she broke down completely with increasing cough, fever and hemoptysis, and lost 10 pounds. She stayed at Arequipa fourteen months, and improved, then went to Los Gatos for seven months, at the end of which time she weighed 180 pounds, she then returned to Arequipa for five months. She came to San Francisco in February, 1919, and felt quite well. She had a moderate amount of sputum, some dyspnea, and occasional fever. By the end of 1919, she had lost 12 pounds and had fever, dyspnea and cough. From February to October, 1919, she had an artificial pneumothorax (fifteen injections) and felt well, but



Fig. 23 (Case 4)—Before operation. Large cavity upper right with fluid level. Pyopneumothorax below with fluid level and small gas bubble. Heart and trachea drawn far to right.

the sputum remained the same. Nov. 8, 1920, she had pleurisy and fever. From January to April, 1921, pus was removed from the chest by Drs. Richter and Whitney and the chest was irrigated. Her average weight was 160 pounds, weight on entrance to the San Francisco Hospital was 135 pounds.

*Examination*—The right chest is retracted and moves less than the left. There is a little expansion in an anteroposterior direction on the right side of the sternum, at the third and fourth ribs, but there is no anteroposterior expansion of the lower right chest. There is no transverse expansion on the right side. There is a cavity at the right apex and below it a pneumothorax with a succession splash. The mediastinum lies one inch to the right of the midline. The trachea enters the sternal notch one-half inch to the right. The respiration is wheezy. She expectorates mainly in the morning on sitting up from a recumbent position. When sleeping on the left side she coughs, but attempts to make her cough by lying on her left side, or by hanging her head over the bed, are unsuccessful. Her heart is displaced to the right. Her



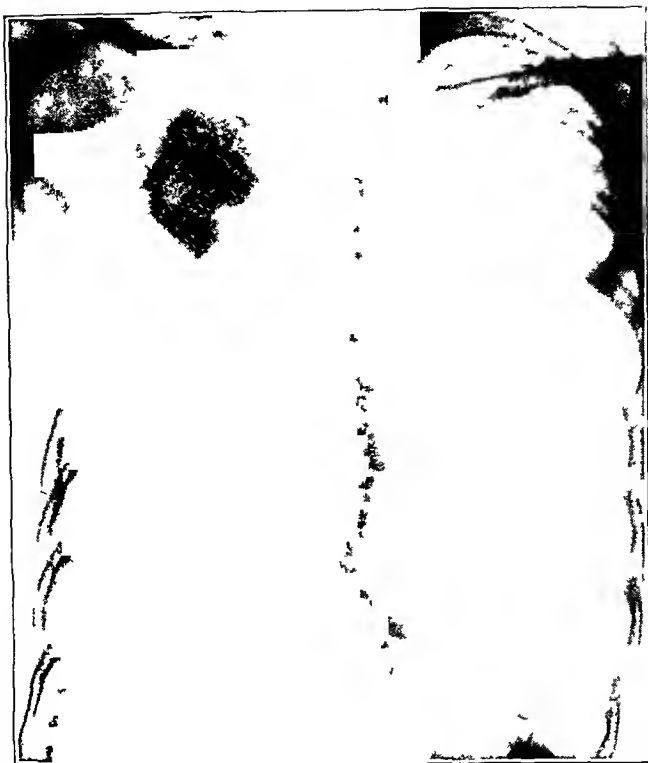


Fig 24 (Case 4) —One month after operation Distal stumps of first and second ribs in second intercostal space Cavity persists, but is smaller, no fluid level Dense shadow lower right chest Trachea not distinct, probably to left of midline

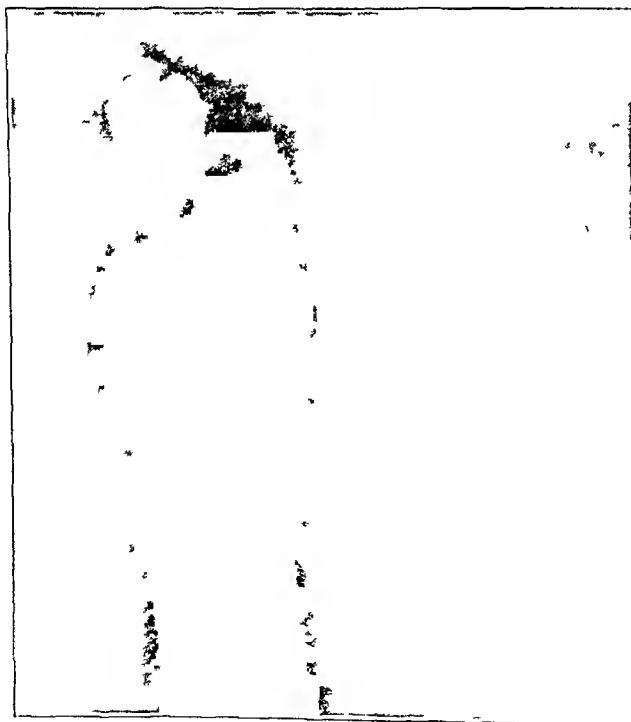


Fig 25 (Case 4) —Nine weeks after operation Cavity persists but is smaller No fluid level No evidence of fluid lower chest

fingers are clubbed Her sputum averages 140 c c per day Aspiration in the seventh intercostal space, below the scapular angle, yields 30 c c of pus swarming with tubercle bacilli On forced expiration no air comes from the needle, but a little bubbles in when the patient breathes quietly

*Diagnosis* — Chronic fibrous phthisis, with large cavity in upper right lung and pyopneumothorax below

Aug 11, 1921, some methylene blue was injected into the empyema cavity which was not coughed out in two days, showing that there was no bronchial fistula August 17 the urine was stained green

*Treatment* — FIRST OPERATION Aug 15, 1921, under satisfactory local anesthesia, the twelfth to the first ribs were resected More was taken of the third, fourth and fifth ribs in order to compress the upper parts of the lung more

The resected pieces measured First rib, 2 cm, second rib, 4 cm, third rib, 6 cm, fourth rib, 8 cm, fifth rib, 8.7 cm, sixth rib, 11.4 cm, seventh rib, 7.8 cm, eighth rib, 7.2 cm, ninth rib, 7.5 cm, tenth rib 7.3 cm, eleventh rib 5.7 cm, twelfth rib, 4 cm

*Course* — A week following operation the sputum measured from 20 to 25 c c A month later the sputum began to increase in amount, and Sept 27,

TABLE 4—SUMMARY OF DATA IN CASE 4

	Temperature, F	Pulse	Respiration	Sputum, C c	Weight, Pounds
Before first operation, Aug 15, 1921	97-99.5	80-105	20-28	140	135
August 16 to September 1	98.0	90	20	33	?
September 1 to October 1	97-98.6	80-90	25	120*	?
October 1 to November 12	97-98.6	75-90	25	110	125
Second operation, Nov 12, 1921	97-98	85-95	25	40	128
Nov 12, 1921, to Jan 1, 1922	97-98.6	75-90	25	30	<133
January 1 to March 9					
Influenza					
March 9 to March 20	98.6-101.5-98-99	85-100	20-25	125	133
March 20 to June 1	97-98.6	80-90	20-25	105	133

Blood Hemoglobin, 75 per cent red blood cells 5,500,000, white blood cells, 15,000, polymorphonuclears, 63 per cent, small lymphocytes, 33 per cent, large lymphocytes, 2 per cent, mononuclears, 2 per cent, basophils, 0.5 per cent

\* Increased from 30 to 200-400 toward last week of September

1921, a distinct succussion splash was heard at the sixth rib The patient had noticed this herself Oct 3, 1921, the chest expansion was, 75-77.2 cm = 2.2 cm

Roentgen-ray examination, Oct 21, 1921, showed no movement of the diaphragm on Valsalva's experiment<sup>19</sup> The right side of the chest was absolutely quiet The cavity was not influenced by normal pressure on the chest

Nov 12, 1921, the signs of cavity and increased expectoration still persisted

SECOND OPERATION — Under satisfactory local anesthesia a curved incision was made over the middle of the right clavicle and carried downward to the fourth rib The clavicle was cut through with a Z-shaped incision and the vessels and plexus were retracted The fourth to the first ribs were resected from the mamillary to the axillary line The site of the previous posterior resection had united so that the middle piece of the ribs could not be avulsed when they were cut through in front The chest was well collapsed over the third and fourth ribs The first two ribs, however, bulged out over the level of the flat chest like a dome The clavicle was united with kangaroo tendon

The resected clavicle measured 2.8 cm, first rib, 2 cm, second rib, 4.7 cm, third rib, 5.5 cm, fourth rib, 6 cm

19 Forced expiration against the closed glottis



Kink of  
Trachea

Cavity

Fig 26 (Case 4) —Five weeks after second operation Collapse much increased, especially of upper part of chest A small narrow cavity still visible here Marked improvement right lung Trachea distinctly to right of midline It is kinked to the right at the level of the top of the sternum



Fig 27 (Case 4) —Seven months after second operation The right chest is much narrower and the ribs steeper than in the previous figure The difference is especially noticeable in the lower part of the chest The ribs run almost vertically The peripheral ends of the first and second ribs lie in the second intercostal space The trachea is in the midline The clear space below the right clavicle is possibly, but not certainly, the remains of a cavity The clavicle has united The figure is a combination of two films one overexposed for the collapsed side one normally exposed for the good side

*Course*—Dec 3, 1921, the patient sat up. The sputum was 30 cc per day. By December 7 the sputum had increased to 60 cc.

Jan 20, 1922, the roentgen-ray showed a satisfactory compression. The right diaphragm was obscured. The heart shadow was compressed against the right rib cage.

February 16, the roentgen-ray showed no respiratory expansion on the right side. The heart and mediastinum were displaced to the right. The left chest was normal in appearance and respiratory excursion (Dr Chamberlain).

March 6, she had otitis media, and March 10, she had an attack of influenza.

March 24, the roentgen ray showed that the right side of the diaphragm moved slightly in the same direction as the left side. The mediastinum did not shift during expiration. The right chest was completely collapsed. There was no aeration of the right lung.

April 27, the vital capacity was 1,250 cc.

May 12, the roentgen ray showed that the right diaphragm moved less than the left but in the same direction. The right lung was well collapsed. The mediastinum moved to the right on coughing. There was a dense pleural scar in the lower right axilla.

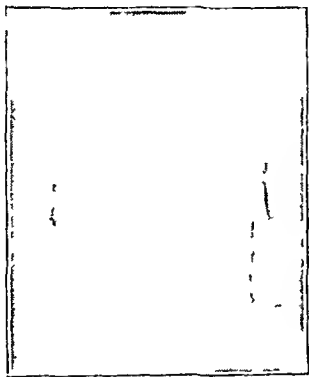


Fig 28 (Case 4)—July, 1922, eight months after second operation, showing retraction of right chest.

June 2, roentgen ray showed no collapsing spaces (cavities) in the right chest. There were old scars of the left hilus and lung. The right side of the diaphragm moved with the left as far as it could be seen.

June 24, she had a subcutaneous tuberculous abscess under the right scapula. The abscess was aspirated. There were no signs of empyema.

The sputum showed tubercle bacilli August 2, September 20, September 30 and Oct 31, 1921.

The urine was negative. The Wassermann reaction was negative.

*Additional Notes*—The patient is still in the hospital. The subcutaneous cold abscess which appeared June 24 doubtless came from a breaking through of the old empyema, although she has had no other empyemic signs. The succussion splash disappeared after the first collapsing operation and was last heard Sept 28, 1921 (six weeks after the first operation). We thought that the continued sputum might be due to a perforation of the old empyema into the lung, but repeated examinations with this in view gave no positive evidence.

July 19, 1922, the cold abscess was incised under local anesthesia and about 100 cc of green pus with thick flakes of fibrin were removed. The incision was closed. Immediately after closing the incision the patient coughed and the abscess refilled, it doubtless communicates with the old empyema but not with the lung. It was irrigated with iodine, the patient neither coughed out the iodine nor tasted the fumes.

The cavity is smaller, but still persists. A third operation, probably an intrapleural direct compression of the cavity, may be undertaken. The patient is up, has no fever, and looks and feels much stronger than before operation. The outcome is doubtful.

**CASE 5**—Miss B. N., student, aged 26, was referred by Dr. Philip King Brown to the San Francisco Hospital. She was in the hospital from Oct. 4, 1921, to March 16, 1922.

**History**—The patient lived in the same house with a sister who died of tuberculosis twelve years ago. She has had a cough off and on for six years, which has been incessant for the last three years, with occasional blood-tinged sputum. She was in New Mexico for two years and ten months, and in July, 1920, entered Arequipa, in October, 1920, she was discharged unimproved.

During August and September, 1920, Dr. Mentzer made three attempts at pneumothorax. On the first attempt 100 cc of air went into the neck, on the second attempt, 250 cc of air went into the neck, and on the third attempt, all the air (250 cc) went into the neck.

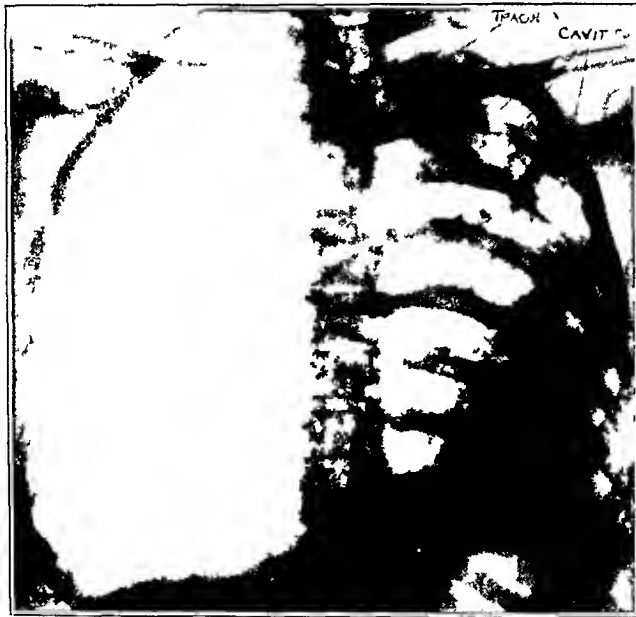


Fig. 29 (Case 5)—Before operation. Multiple cavities upper left. Trachea strongly retracted to left and curved at its entrance under the sternum. Calcified areas right.

Her tonsils were removed Oct. 2, 1921, before that she had occasional attacks of sore throat.

She was admitted to the San Francisco Hospital Oct. 4, 1921.

**Examination**—The left side moved less than the right. There were fair movements above (second and third intercostal spaces), in an anteroposterior direction but the transverse movement was small, one-half that of the right side. The trachea entered the sternal notch one-half inch to the left. There was flatness from the middle of the left scapula downward, and there were creaks and rales all over the left side. The heart beat was palpable posteriorly below the angle of the scapula, at the bottom of a space that gave amphoric breathing and a clucking sound synchronous with the heart beat. There were crepitations at the right apex (possibly pleural) and a few fine rales after coughing. The blood pressure was 112/65. The roentgen ray showed dif-



Fig 30 (Case 5) —Six weeks after operation Cavities no longer visible Trachea straight, but still slightly to left of midline No scoliosis Peripheral stump of first rib is in third interspace



Fig 31 (Case 5) —Four and three-quarter months after operation March 21, 1922 Marked scoliosis toward the affected side Trachea is in midline Increasing dilatation is noted in right side of chest Stump of first rib is in second interspace Central stumps of first, second and third ribs and distal stump of first rib are united by bony callus The left chest, especially at its top, is narrower than in the previous figure

fuse fibrosis on the left side, and considerable infiltration and calcified masses at the right top. The chest expansion over the lower scapula was 79-77 cm = 2 cm, the vital capacity, 1,800 c c

*Treatment*—November 1, resection of all the left ribs at the costal angle was done. The heart lay beating between the scapula and the posterior axillary line, being drawn far toward the back and the left side, the action was stormy. With the patient on her right side, the second rib lay higher than the first. The lateral part of the latissimus dorsi was inverted with two or three mattress stitches so that its cut edge was under the central stumps of the ribs. This was done to aid the dislocation of the posterior edge of the scapula forward under the posterior stumps of the ribs. The patient was returned to bed with a thin fleeting pulse and shallow respiration.

The resected ribs measure: First rib, 25 cm, second, 43 cm, third, 83 cm, fourth, 82 cm, fifth, 96 cm, sixth, 10 cm, seventh, 107 cm, eighth, 8 cm, ninth, 8 cm, tenth, 75 cm, eleventh, 78 cm, twelfth, 35 cm. The following day she had a very rapid pulse, but was better toward evening.

*Course*—December 3, the patient had pain in her shoulder when she moved her head. There was bronchial breathing all over the collapsed side. This side moved a little in the upper anterior quadrant, but not below. The posterior



Fig. 32 (Case 5)—Six months after operation. Retraction of left side of chest.

edge of the scapula lay considerably in front of and medial to the medial fragments of the ribs. She was allowed to sit up one-half hour a day, which caused no increase of sputum. Jan. 17, 1922, she had otitis media.

February 16. In the posterior axillary line, at about the fifth rib, there was amphoric breathing with a few distant moist râles. The left lung was well collapsed, though part of the cavity probably persisted. The patient was generally much improved (Clark).

TABLE 5—SUMMARY OF DATA IN CASE 5

	Tempera- ture F	Pulse	Respira- tion	Sputum, Cc	Weight, Pounds
Before operation, Nov. 1, 1921	98-99.5 occasionally to 100	80-100	25	28, daily regularly	116
Two weeks after operation	98.6-100	100-110	23	10	?
December	98.6-99.5	90-100	25	5	108
January, 1922	97-98.6	85-110	30	5-10	112-115
Present	Normal	Normal	Normal	About 4	124

Urine negative

Blood Hemoglobin 80 per cent, red blood cells, 4,500,000; white blood cells, 11,800; polymorphonuclears 75 per cent, small lymphocytes 15 per cent, large lymphocytes, 10 per cent, transitionals 1 per cent, eosinophils 1 per cent.

TABLE 1—SUMMARY OF DATA OF FIVE CASES OF IDIOPATHIC COMPRESSION

Patient	Involvement	Pneumothorax	Weight		Temperature		Sputum		Tb bacilli		Vital Capacity		Im- proved
			Before	After	Before	After	Before	After	Before	After	Before	After	
1 Mrs M M	Cavity left apex, slight in- volvement right apex	Unsuccessful	115	120½	98-100	97-98.6	25-30	0	+	—	?	?	+
2 Miss F W	Cavity right, serous pleu- risy with adhesions	12 attempts, partial success	176	162	98-99	98-99	50-100	10-12	+	—	?	?	+
3 Miss T T	Right 3 cavities slight in- volvement left apex	3 attempts unsuccessful, 1 attempt 75 cc	130	125	98-100	98-99	40	1st 20 2d 17½ 3d 16	+	+	?	1st 1,550 2d 1,400 3d ?	+
4 Miss K O	Large cavity upper right, pyopneumothorax lower right	Pyopneumothorax lower chest does not influence cavity	135	133	97-99.5	97-98.6	140	1st 33<120 after influenza 2d 40<120	+	+	?	1st ? 2d 1,250	+
5 Miss B N	Diffuse fibrosis with cavity left apex, enlarged spots right hilus, infiltrate right top	3 attempts unsuccessful	116	124	98.6-100	97-98.6	28	4	+	—	1,800	1,350	+

Note November, 1922 Apparent cure of Cases 1, 2 and 5 continued improvement of Cases 3 and 4



February 17, the roentgen ray showed no respiratory excursion of the left ribs. The left diaphragm moved with the right, but with a markedly diminished excursion. The right lung was clear, except for calcified small spots. The mediastinal contents were displaced to the left and did not move even on forced respiration (Chamberlain).

February 25, the patient had a sore throat and headache.

March 16, she was discharged to her home.

Wassermann negative.

The sputum showed tubercle bacilli Nov. 1, 1921. Five examinations in July, 1922, were negative.

Spirometer. Before operation, 1,800 c c, after operation, 1,350 c c.

July, 1922. The patient has been up for about six hours a day, has gained 16 pounds in weight, has good color, and feels strong and well. She still has about 4 c c of watery sputum a day, which on five examinations contained no tubercle bacilli. She is probably cured.

It is too early to judge of definite results. This much, however, can be said. None of the five patients has been harmed. All of them have been improved, and their sputum has diminished. Three seem to be cured.

#### CONCLUSIONS

1. Operative collapse of a tuberculous lung is indicated in mainly unilateral tuberculosis, when an artificial pneumothorax is indicated but cannot be carried out effectively.

2. Chronic fibrous phthisis, with thick pleural deposits and a rigid chest wall, offers the most frequent indication.

3. Operation should be decided on only after close observation and study of each patient, after repeated consultations with a competent internist, and after attempts at compression by means of pneumothorax have failed.

4. The procedure of choice is (a) Sauerbruch's total thoracoplasty, or (b) partial pneumothorax with partial thoracoplasty.

5. Operation should be done under local anesthesia.

6. Some patients will be cured by operative collapse after other treatment has failed.

# QUANTITATIVE STUDIES IN SYPHILIS FROM A CLINICAL AND BIOLOGIC POINT OF VIEW

## II NORMAL ARSENIC ~

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In the previous article <sup>1</sup> we described in detail a method of determining quantitatively minute amounts of arsenic in biologic material. In order that a conclusion not influenced by a normal variation can be obtained from this series of analyses, it has been necessary to make a study of the possible arsenic content both in patients who are receiving and in those who have never had any treatment whatever in which arsenic is used as a remedial agent.

The ingestion of foods prepared by artificial processes, fruits which may have been sprayed with arsenical solutions, sea food which in some localities is contaminated to a large degree with arsenic, copper, etc., candy made from glucose, together with a large variety of other possibilities of arsenic ingestion, makes it necessary to gain some idea as to the "normal" arsenic content among our patients. Gautier and Clausmann <sup>2</sup> analyzed a variety of food articles, meats, milk, eggs, fish, shellfish, vegetables, wines, from whose arsenic content they estimate that each inhabitant of Paris receives 7.66 mg arsenic per annum in his food. Water supply and air also contribute to the possibilities of the presence of arsenic. Brewers quite generally used glucose, which probably was responsible, for some, at least, of the cases of "arsenuria." Arsenic is also occasionally found in baking soda, glycerin, syrups, magnesium sulphate (Epsom salts), sodium sulphate, (Glauber's salt), bismuth subnitrate, and other medicinal products. We also have the

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1 Fordyce, J. A., Rosen, I. and Myers, C. N. Quantitative Studies in Syphilis from a Clinical and Biologic Point of View, *Am J M Sc* **164** 242, 1922

2 Gautier, A. Arsenic dans des eaux de mer, dans le sel gemme, le sel de cuisine, les eaux minerales, etc. Son dosage dans quelques reactifs usuels, *Compt rend* **137** 232, 1903. L'arsenic existe-t-il dans tous les organes de l'economie animale? *Compt rend* **137** 295, 1903. Origines alimentaires de l'arsenic normal chez l'homme, *Compt rend* **139** 101, 1904

famous beer drinkers' cases in England in 1900. These reports are found in articles by Helmer,<sup>3</sup> Reynolds and the Royal Commission.<sup>4</sup>

These brief references to the possibilities of finding arsenic in the patients in this locality make it imperative to give some attention to the proper control of normal arsenic content.

A short historical reference to the normal arsenic content will clarify some of the findings which are obtained when only a casual study is made.

Couerbe<sup>5</sup> announced to the French Academy that he had found traces of arsenic in the putrid bodies of human beings. Orfila,<sup>6</sup> Devergie, and others (1838-1840) energetically defended the statement that arsenic was a normal constituent of human bones. In 1841, Orfila and Devergie abandoned their belief in "normal" arsenic as a result of the denial of the truth of these views by Flandin<sup>7</sup> and Danger,<sup>8</sup> as well as recognizing as a result of further analyses that their previous determinations were affected by error. This error emphasizes the necessity for great care in selecting very pure reagents, a fact that has been given very considerable thought throughout this entire investigation. Devergie attributed his findings to the existence of traces of arsenic in his reagents and to the great delicacy of the Marsh test. Orfila regarded it in the light of "history of the so-called normal arsenic as an impenetrable mystery."

The question then lay dormant until 1899 when Gautier<sup>9</sup> presented a series of papers to the French Academy in which he claimed that arsenic is a normal and consistent constituent of the thyroid, mammary glands, brain, thymus, hair, skin, milk and bones of man and of herbivorous and carnivorous animals. The amounts present in the various organs were given as follows: thyroid, 0.76 mg in 100 gm tissue, mammary gland, 0.13 mg in 100 gm tissue, brain, variable quantity, or none. Tissues from hog, sheep and man were examined. In the

3 Helmer, O. Discussion on the Occurrence and Detection of Arsenic in Manufactured Products, *J Soc Chem Ind* **20** 189, 1901.

4 Royal Commission. The Royal Commission on Arsenical Poisoning, *Brit M J* **2** 1483, 1557, 1610, 1903. The Final Report of the Royal Commission on Arsenical Poisoning, *Lancet* **2** 1674, 1746, 1903.

5 Couerbe, J. P. Du cerveau considere sous le point de vue chimique et physiologique, Paris, E. J. Bailly et Cie, Reprint from *Ann de chim et phys* **56** 1934, 1834.

6 Orfila, P. Traite des poisons tires des regnes mineral, vegetal, et animal, ou toxicologie generale, considerée sous les rapports de la physiologie, de la pathologie et de la medecine legale, Paris, 1852, Labe, 5 de.

7 Flandin, C. Traite des poisons, ou toxicologie appliquee a la medecine legale, a la physiologie et a la therapeutique, Paris, Bachelier, 1846-1853.

8 Danger, E. P. and Flandin, C. De la localization des poisons. Note adressee a l'Academie des sciences en reponse a un article de M. Orfila, Paris, 1844.

9 Gautier, A. Sur l'existence normale de l'arsenic chez les animaux, et sa localisation dans certains organes, *Compt rend* **129** 929, 1899.

normal blood Gautier believes the amount does not exceed 1 50,000,000 or 0 00000002 gm metallic arsenic Bertrand,<sup>10</sup> Schaefer,<sup>11</sup> Pagel,<sup>12</sup> Knecht and Dearden<sup>13</sup> and Segale (1904) confirmed the results of Gautier

The translator of "Detection of Poisons" by Autenrieth (1921) having carefully examined the literature also regarded the subject of sufficient importance to discuss it to considerable extent Following Gautier's report to the French Academy, a committee of that body examined the existing results and arrived at a conclusion as follows

Speaking from a medicolegal point of view, I would state that arsenic, aside from the thyroid, mammary and thymus glands, never occurs in the human body except in the skin, hair, bones, milk and sometimes in the feces and then only in traces which are often infinitesimal Excepting the brain, the other organs and fluids, especially those forming the bulk of the body, as muscular tissue, liver, spleen, kidneys, lungs, blood, urine, etc, fail to show the slightest trace of arsenic If a chemist therefore examines individually these arsenic-free organs by my method or by one less delicate and finds traces, especially appreciable traces, of this metalloid, such arsenic has been absorbed during life either medicinally or criminally

Observer	Material	Arsenic Found	Remarks and Conclusions
Gautier	Human and animal organs and other material	0.75 mg in 100 gm of human thyroid gland	Used six glands and assumed uniform distribution of arsenic
Bertrand	Only animal material	0.015 mg per 100 gm of dried sponge	Concludes arsenic is a normal constituent of protoplasm
Schaefer	Human organs	0.007 mg per 100 gm of human thyroid	Concludes arsenic may occur in all organs but found many free from arsenic
Pagel	Human and animal organs	Positive but not quantitative	Found testes arsenical but Gautier says they are not

On the contrary, several chemists have carefully analyzed human and animal organs, either finding no arsenic or detecting this metalloid in mere traces, which are inconstant in occurrence and confined to no special organ The table on this page briefly summarizes their results

The results set forth in this table place "normal arsenic" in a doubtful position at least If it is a reality and not a fancy, the quantity of arsenic, compared with that obtained in an analysis actually dealing with this metalloid, is so minute that the toxicologist need feel no concern If he has con-

10 Bertrand, G Sur l'existence de l'arsenic dans la serie animale, Bull de la Soc Chim de Par **27** 1233 1902, Compt rend **135** 809 1902 Sur l'existence de l'arsenic dans l'organisme, Compt rend **134** 1434, 1902 Nouvelles Recherches sur l'arsenic de l'organisme Presence de ce Metalloide dans la Serie Animale, Ann de l'Inst Pasteur **17** 1, 1903 Sur l'existence de l'arsenic dans l'oeuf de la poule, Compt rend **136** 1083, 1903 Emploi de la bombe calorimetrique pour demontrer l'existence de l'arsenic dans l'organisme, Compt rend **137** 266, 1903

11 Schaefer, G Recherches sur l'existence normale de l'arsenic dans l'organisme humain, Ann chim anal **11-12** 52, 97, 1906

12 Pagel, J L Dissertation, 1900, University of Nancy

13 Knecht, E, and Dearden, W I The Elimination of Arsenic Through the Hair and Its Relation to Arsenical Poisoning, Lancet **1** 854, 1901

ducted his analysis with every precaution as regards reagents and method and obtained a distinct mirror, he may dismiss the "normal arsenic" chimera and accept the result as due to arsenic that has entered the body from some external source. Kunkel has summed up the matter in these words:

"The so-called normal arsenic, if there is such a thing, does not effect the results of forensic chemistry, because the so-called normal quantities are so exceedingly small (0.01 or even 0.001 mg in an organ) that the quantities necessary to furnish a satisfactory forensic proof, which are a hundred or even a thousand times greater, must be regarded as an entirely different and much higher order of magnitudes."

In direct contradiction to the results of Gautier, Ziemke<sup>14</sup> obtained contradictory results.

In discussing the divergence between his results and those of Gautier, Ziemke considers that there can be no error of manipulation or question of the purity of reagents in the work of the French toxicologist, because of the uniformly negative results which he obtained with organs other than those mentioned, and he attributes the difference in the results attained, firstly, to the known fact that certain organs take up arsenic more readily and retain it more persistently than others, and, secondly, to the fact that in Germany, under existing laws, articles of food, condiments, etc., are subject to a very strict supervision and that the possibility of the introduction of arsenic into the system by this means is very slight, while in other countries arsenic is frequently found in articles used in the household and also in food products. He cites the statement of Shattuck that in the United States the urine of many healthy persons contains arsenic, which, according to Richter is not the case in Germany. This may account for the presence of arsenic in the thyroids of man, or even of the dog and hog, but hardly for that found in the sheep.

This statement is attributed to Shattuck by many writers, particularly among the Germans. It is, however, not original with him, but is a quotation from Putnam (Boston M & S J **122** 421, 1890), who states that of forty-eight samples of urine collected at random from the outpatients at the Massachusetts General Hospital, twenty-one were found to contain traces of arsenic. Shattuck's paper is the report of an address favoring the passage of legislation in Massachusetts to restrict the use of arsenical pigments in the manufacture of wall papers, and Putnam's observations were apparently prompted by the same interest, and although he states that these patients "did not present any symptoms which seemed referable to arsenical poisoning," they were certainly not "healthy," and there is no assurance that they had not been exposed to arsenical contamination. One of the alternatives suggested by Abel and Bittenberg (Ztschr f Hyg **32** 478, 1899), in referring to Shattuck namely, that "people in America deal carelessly with arsenic," would very probably have been accepted by both Shattuck and Putnam as a more reasonable explanation of the presence of arsenic in these urines, than the hypothesis of "normal arsenic," which was not entertained at that time.

There is no irreconcilable contradiction between these apparently inconsistent results from a medicolegal point of view, although there may be from that of physiology. Gautier's supposition that arsenic is a "normal" element of certain tissue constituents, and plays a part in their functioning, like the iodine in the thyroid is clearly negatived if it be shown not to be a constant constituent of those tissues. That question is one of notable interest to the biological chemist but it does not concern the toxicologist to whom it is immaterial whether arsenic found in these minute quantities with great

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14 Ziemke, E. Ueber Vorkommen von Arsen in menschlichen Organen und seinen Nachweis auf biologischem Wege, Vierteljschr f ger Med **23** 51, 1902

frequency in certain organs, not usually submitted to analysis in forensic cases, is normal or of fortuitous origin

There can be no doubt, however, that arsenic is very widely distributed in nature and is constantly taken into the human economy in very minute quantities. Gautier has found that sea salt contains from 0.001 to 0.045 mg arsenic in 100 gm, and rock salt from 0.0025 to 0.014 mg. Sometimes these arsenic values are of such nature as to affect entire communities as when the water supply or air contains arsenic. Or certain individuals only in a community may absorb arsenic from food articles more highly arsenical than those referred to above as in the Manchester beer poisonings. Several investigations in which delicate and direct methods of examination were used, and the purity of the chemicals was assured, have shown that the presence of arsenic in human urine, in quantities very rarely exceeding 0.1 mg per liter, and in the absence of any history of its administration, is by no means unusual, at least in Boston and its vicinity, and we have no reason for supposing that conditions differ there in this regard from what they are in other cities in the United States. Putnam found arsenic in 30 per cent of 150 samples of urine examined. Sanger detected arsenic in twenty cases, and Hills, examining 260 samples from 180 patients, found arsenic in 135 or 75 per cent. In five of these cases Hills found exceptionally as much as from 0.3 to 0.5 mg per liter. In many of the cases the origin of the arsenic was traceable to arsenical wall hangings, etc., but in others it could not be so accounted for. Hills suggests that the very general use of Paris green as an insecticide, may have produced an arsenical impregnation of the soil in certain localities, from which growing vegetables might become contaminated.

Gautier and Clausmann<sup>15</sup> studied the methods of destroying organic matter, and Gautier<sup>16</sup> revised some of the results published in 1899<sup>9</sup> and 1903<sup>3</sup> with reference to the quantity of arsenic in normal tissues and thinks that the error was due to traces of arsine in the hydrogen sulphid which was used for precipitating the arsenic. In this paper, the results of Gautier's previous experiments are reviewed in relation to the traces of arsenic which had been previously discovered in tissues. In his former investigations, the quantities of arsenic which had been reported were a trifle too large, due to the error which has just been mentioned. The mention of this fact does not modify essentially the first conclusions on normal arsenic, its localization and mode of elimination, but has resulted in a revision of the method of destruction of tissues used in medicolegal experiments. In conclusion, Gautier points out that it should be proved beforehand that there are no detectable quantities of arsenic in the nitric, sulphuric, and hydrochloric acids used.

Bloemendal<sup>17</sup> found that normal urine contained traces of arsenic and that traces may be found under normal conditions in the body of

<sup>15</sup> Gautier, A., and Clausmann. A New Method for the Destruction of Tissues for the Detection of Arsenic and the Examination of Their Ashes. *Compt rend* **165** 11, 1917.

<sup>16</sup> Gautier, A. On Normal Arsenic in Living Tissues, and Traces of Iodine Found in Air and Water, *Compt rend* **170** 261, 1920.

<sup>17</sup> Bloemendal, W. H. Arsenic in the Animal Organism, *Arch Pharm* **246** 599, 1909. Arsenical Poisoning in Vineyards, *Brit M J* **2** 86 (July 16) 1921.

man and animals but that it has no physiologic significance. As a result of his work he concluded that arsenic does not pass into the foetal circulation.

Bang<sup>18</sup> found arsenic in normal urine in twenty-five cases in daily amounts up to 0.5 mg. Only in three cases was arsenic not found. The greatest amount of arsenic in the urine was found after a fish diet. During the use of a vegetable and milk diet, the urine is usually free from arsenic.

Klason<sup>19</sup> draws the conclusion that arsenic is a normal constituent of the human body. Klason examined the urine of a man who had never taken arsenic in any form, nor had he suffered from "arsenic sickness." He found that the urine of this man always contained arsenic to the extent of from 0.005 to 0.0125 mg. per liter. Klason states that the methods which have hitherto been used for the estimation of arsenic in organic secretions are so inexact that the results obtained are open to criticism.

McNally<sup>20</sup> investigated the retention of arsenic in two cases in which arsenic had been administered. The results are expressed in grams of arsenous oxid in 100 grams of the tissue. In the first case the man died four and one-half hours after taking an unknown amount of some form of arsenic. The amounts are: stomach walls, 0.0328 gm., stomach contents, 1.1782 gm., liver, 0.0191 gm., small intestine, 0.0176 gm., large intestine, 0.0345 gm., left kidney, 0.0122 gm., right kidney, 0.0108 gm., heart, 0.0085 gm., pancreas, 0.0125 gm., lung, 0.0027 gm., gallbladder, 0.0055 gm., esophagus, 0.0224 gm., brain, 0.00026 gm. In the second case the results are on a patient who died ten days after the last dose of an arsenical. The death is reported as typical of arsenical poisoning. The results of examination of tissues for arsenic were as follows: spinal cord, 0.00275 gm., blood, 0.0066 gm., stomach wall, 0.00066 gm., stomach contents, 0.00066 gm., kidney, 0.00211 gm., spleen, 0.00171 gm., liver, 0.00171 gm., urine, 0.00363 gm.

Generally speaking, conflicting reports, whether positive or negative, are usually based on the quotation "if arsenic were a normal constituent, there could be no exception, and therefore its presence in the cases in which it has been found must be adventitious."

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18 Bang, I. The Amount of Arsenic in Normal Urine, *Allm. Sv. Läkaretidn.* **13** 549, 1916. Quantitative Determination of Arsenic in Urine, *Schweiz. Apoth. Ztg.* **55** 393, 1917.

19 Klason, P. Quantitative Determination of Arsenic in Organic Secretions and Compounds, *Ark. Kemi. Min. Geol.* **5** 9, 1914. Determination of Small Amounts of Arsenic and the Normal Arsenic Content of Urine, *Svensk Kem. Tidskr.* **28** 69, 77-80, *Ark. Kemi. Min. Geol.* **6** No. 6, pp. 1-5, 1916. Quantitative Determination of Arsenic in Organic Secretions and Compounds, *Ark. Kemi. Min. Geol.* **6** 1, 1916.

20 McNally, W. D. Retention of Arsenic in the Organs, *J. Am. Chem. Soc.* **39** 826, 1917.

We do not accept nor do we resort to this argument. As pointed out in the beginning of this article, diet was recognized as a source of arsenic and on this basis the history of each patient shows in a general manner the nature of the diet consumed. Direct personal contact with careful records, as given in the data below, has assisted us materially in arriving at the results which are contained in this article.

The results of investigation can only affirm or cast doubt on the presence or absence of arsenic as a normal constituent. In order to control these factors of food and medication satisfactorily, careful histories have been taken on all the patients. More detailed discussion of each table and its clinical aspect will be found later. The discussion of the charts will only refer to the normal arsenic aspect of this series of articles. Control methods have been employed throughout this investigation and conclusions are arrived at only after an extensive examination of a large group of patients so that the errors due to the biologic economy are reduced to a minimum. A one-patient or a two-patient study will add little accurate knowledge with a wide application to others. The composition of some of the drugs used by the patients has been investigated in relation to the arsenic content, likewise glucose, a common article of food in beverages, delicatessen products, ice creams, candy, and bakery products, was examined. The latter proved interesting in its application to a few patients who, it was presumed, were on a sugar-free diet. Three samples of glucose were examined for arsenic and it was found that only the purest preparation was free of arsenic. Sample 2 contained 0.778 mg arsenic per hundred grams, and sample 3 contained 0.10 mg arsenic per hundred grams. These figures found ready application to a series of patients using food products containing glucose syrups and bakery supplies as well as to candy eaters who indulged to a considerable extent. Glycerol, a constituent of some rhubarb and soda, is another important product to be considered. The other drugs will be noted in a table showing the remedies used.

#### RESULTS OF EXAMINATION

*Normal Hair*—Hair from twenty-one persons, fifteen men and six women, was examined for arsenic. In nine specimens no arsenic was detected, in twelve arsenic in amounts varying from 0.052 to 10.6 mg was found. In the cases showing the smaller quantities no definite data were obtainable to determine the source of the arsenic, that is, whether any preparation had been employed on the scalp or whether ingestion, environment, occupation, etc., were responsible.



Specimens 1722 and 1723 were from husband and wife, the larger amount being from the latter. Investigation proved that both were using a hair tonic in which arsenic was a contamination of one of the ingredients. The blood and urine in these cases were arsenic free.

TABLE 1—ARSENIC IN NORMAL HAIR

Patient Serial No	Weight of Specimen, Dry	Arsenic in Mg per 100 Gm of Specimen	Patient Serial No	Weight of Specimen, Dry	Arsenic in Mg per 100 Gm of Specimen
1612	1.3427	0.992	1723	0.1944	3.08
1629	3.0808	None	1627	0.4634	None
1614	2.5777	None	1610	1.6476	10.6
1720	0.8428	0.0593	1628	1.7961	0.280
1630	0.5541	None	1495	1.1003	None
1725	0.7362	None	1626	0.6561	None
1721	1.9112	0.0523	1613	3.1559	0.950
1611	1.7902	None	1731	0.2993	0.166
1496	1.7685	0.452	1783	1.6400	0.180
1497	0.5500	None	1816	1.5984	0.063
1722	1.2427	2.14			

Specimen 1610, with 10.6 mg arsenic, can be traced directly to contact with arsenic, this hair being obtained from one of the chief chemists of a large drug manufacturing concern whose work was largely connected with the arsenicals. Specimens 1496, 1612, 1613, 1628 and 1731 were also from persons who handle arsenicals. These people all had a thorough shampoo before the hair was obtained so that no mechanical contamination was responsible for the presence of arsenic.

Generally speaking, the hair may contain very small quantities of arsenic but it is questionable if it will be found in more than 50 per cent of persons unless medication plays an important part.

TABLE 2—ARSENIC IN NORMAL HUMAN MILK

Patient Serial No	Weight of Specimen		Percentage Solids	Arsenic in Mg per 100 Gm of Dry Specimen
	Moist	Dry		
1654	6.4550	0.7798	12.08	None
1656	6.9065	0.9313	13.48	None
1648	4.4997	0.5531	12.31	None
1650	5.8792	0.9025	15.35	None
1652	6.6156	0.9261	13.99	None
1657	6.4643	0.9152	14.18	None
1659	6.2585	0.7312	11.68	None
1655	5.1438	0.5346	10.39	0.9
1660	6.2221	0.8489	13.64	0.6
1658	3.2825	0.3650	11.11	None
1651	7.4236	0.9491	12.78	None
1662	4.8614	0.4932	10.24	None
1653	5.3512	0.6885	12.86	None
1649	5.3938	1.5886	10.91	None
1661	4.4750	0.5519	12.33	None

*Human Milk*—It has been shown by several investigators that arsenic when taken in large doses may be secreted in milk. The milk examined in this study was obtained from fifteen nursing mothers in a maternity hospital. They were all healthy women on a mixed hospital

diet of meat, vegetables, cereals and the usual fluids In thirteen cases no arsenic was demonstrable, in two cases (Nos 1655 and 1660) it was present in amounts of 0.9 and 0.6 mg, respectively An attempt to determine whether these patients had been taking tonics containing arsenic was unsuccessful

# RESULTS OF EXAMINATION

*Normal Urine*—These specimens were obtained from persons who denied syphilis or the use of any arsenicals Eighteen specimens were examined, from sixteen men, fifteen white and one black, and two women, one white and one black The ages of these persons varied from 16 to 68 years As to occupation two were chemists, two were students, one was a pharmacist and thirteen were not engaged in any particular line of work

TABLE 3—ARSENIC IN NORMAL URINE

Patient Serial No	Weight of Specimen		Percentage Solids	Specific Gravity	Arsenic in Mg per 100 Gm of Specimen	
	Moist	Dry			Moist	Dry
1480	29.9762	0.5987	1.99	1.015	0.00550	0.278
1131	32.3625	0.9525	2.94	1.018	0.525	17.8
1435	32.0655	1.2091	3.77	1.022	None	None
1140	35.01	0.749	2.14	1.012	None	None
1135	33.243	1.6721	5.03	1.126	0.0525	1.04
1438	32.2200	1.2136	3.76	1.028	0.00931	0.247
1437	32.2435	1.6931	5.25	1.031	0.049	0.915
1310	34.3300	0.8793	2.55	1.016	0.00875	0.34
1481	30.9418	1.7116	5.53	1.037	0.172	3.11
1200	32.0655	1.4783	4.61	1.028	0.00311	0.067
1204	3.134	0.6215	2.00	1.015	0.01064	0.535
1205	31.7606	1.2056	3.80	1.026	None	None
1482	30.9060	1.2838	4.15		None	None
1308	13.1725	1.4668	4.42	1.021	0.0129	0.290
1478	29.7205	0.8481	2.85	1.020	0.0448	1.57
1477	30.0655	1.1484	3.74	1.025	None	None
1479	32.9219	1.7288	5.23	1.030	None	None
1215	32.2435	1.1044	3.43	1.020	0.0036	0.905
1214	32.4375	0.5003	1.54	1.010	0.00306	0.19

Clinical investigation showed that fourteen of these patients were in normal health, that three were tertiary syphilitics and one a primary syphilitic The tertiary syphilis patients were apparently truthful in stating that they had received no arsenical treatment, for arsenic was not present in appreciable amounts in their urine The primary syphilis patient, a young man, aged 21, weighing 115 pounds, admitted exposure four weeks previously and was found to have a chancre on the shaft of the penis behind the corona, in which treponemas were demonstrated by the dark field examination His Wassermann reaction was negative His diet consisted of fish once a week, red meats on the other six days, potatoes twice daily, with other vegetables, eggs and milk in moderation, candy and pastry occasionally His urine on analysis showed 17.8 mg of metallic arsenic From this large amount we can only infer that the patient deliberately withheld the truth regarding previous treatment for his infection and that he must have received an intra-

venous injection of one of the arsenicals elsewhere before coming to our clinic. The presence of so great an amount could be accounted for only in this way.

Three positive results (Nos 1481, 1437 and 1135), the quantities of arsenic varying from 0.67 to 3.11 mg, can be accounted for on dietary grounds. This was nicely illustrated in two cases (Nos 1481 and 1478), two youths, who when the specimens were taken denied having eaten candy or other sweets. When confronted with the results of the examination, however, they both admitted having eaten unusually large amounts of candy for several days prior to the tests. Candy is made largely from glucose which contains varying amounts of arsenic, depending on the quality.

TABLE 4—ARSENIC IN NORMAL URINE

Patient Serial No	Weight of Specimen		Percentage Solids	Specific Gravity	Arsenic in Mg. per 100 Gm of Specimen	
	Moist	Dry			Moist	Dry
1198	32 15	0.2986	0.92	1.010	0.00155	0.16
1306	31 0065	1.4230	4.58	1.023	None	None
1212	32 8334	1.3572	4.14	1.022	0.0031	0.73
1311	35 6495	1.3140	3.68	1.017	0.042	4.4
1312	31 2630	1.2765	4.08	1.021	0.048	1.1
1307	31 3400	1.4810	4.75	1.023	0.0032	0.067
1301	30 6655	1.2790	4.17	1.031	0.0065	0.15
1309	29 7205	1.1965	4.02	1.031	0.027	0.669
1132	84 06	1.552	4.56	1.027	0.00293	0.064
1302	35 2982	0.6007	1.701	1.011	None	None
1317	12 9700	0.2164	1.66		0.123	1.39
1195	32 883	1.5658	4.79	1.028	0.0121	0.255
1197	32 0337	2.0312	6.34	1.033	None	None
1210	30 9785	1.4885	4.81	1.023	0.0193	0.403
1304	31 0271	0.5486	1.71	1.012	0.0016	0.0929
1134	32 4375	2.0249	6.21	1.031	0.00154	0.024
1303	35 330	1.3527	3.82	1.026	0.100	2.5
1136	30 9418	1.0695	3.46	1.021	0.00161	0.0467
1202	31 6773	2.2397	7.07	1.038	0.0526	0.744
1196	32 7995	0.8421	2.59	1.021	None	None
1203	31 3858	0.7203	2.29	1.015	0.4246	18.5
1322	32 2435	1.3065	4.05	1.027	None	None

*Normal Urine and Blood*—In this series of nineteen cases a comparison was made of the amounts of arsenic found in urine and blood taken simultaneously.

There were thirteen men—eleven white, two black—and six women—four white and two black. Their ages ranged from 20 to 55 years. Occupations included four houseworkers, a machinist, an actor, a dressmaker, a shipping clerk, a chauffeur, a tailor, an elevator operator. Five subjects had no occupation.

These patients were selected in the skin clinic after affirming that they had taken no drugs or medicine of any description. This point was especially emphasized as subjects admitting medication were placed in another group. The untrustworthiness of patients' statements, however, is demonstrated in some of the results charted.

The clinical classification is as follows Ten cases of tertiary syphilis with a positive Wassermann only, one case each of early secondary syphilis, seborrheic dermatitis, chromophytosis, pityriasis rosea, sycosis vulgaris, alopecia areata and mucous cysts of the mouth

In the case of secondary syphilis, a white woman, aged 30, dress-maker, there was a generalized circinate papular eruption with leukoderma colli, alopecia of the eyebrows and a generalized adenopathy

TABLE 5—ARSENIC IN NORMAL BLOOD

Patient Serial No	Weight of Specimen		Percentage Solids	Arsenic in Mg per 100 Gm of Specimen	
	Moist	Dry		Moist	Dry
1247	5 7525	1 6580	28 82	0 00569	0 0701
1284	6 1366	1 3701	22 32	0 050	0 21
1328	4 7426	1 2222	25 77		
1289	6 6801	1 3051	21 46	0 0656	0 305
1290	4 6512	0 9413	20 22	0 425	2 12
1285	5 282	1 3838	26 20	0 943	3 6
1099	5 3218	1 1802	22 17	None	None
1288	5 9690	1 6707	28 00	None	None
1287	6 311	1 532	24 28	Trace	Trace
1194	5 8835	1 4986	25 47	0 41	1 6
1241	4 3486	1 1421	26 26	0 269	1 02
1245	5 9133	1 5125	25 58	0 0169	0 066
1286	5 368	1 0405	19 39	0 185	0 66
1103	9 1200	2 3902	26 20	0 022	0 069
1291	5 085	1 4402	28 32	0 039	0 138
1105	6 8352	1 3916	20 35	None	None
1192	5 853	1 2173	20 80	None	None
1246	5 4072	1 2926	23 95	None	None
1175	5 4075	1 2182	22 53	0 185	0 82
1334	4 0060	0 9294	20 70	0 025	0 107

She gave no history of exposure, no evidence of chancre was present, and she denied having had any antecedent treatment She was on a meat-free diet, eating fruit and vegetables in large quantity Her blood showed 1 6 mg arsenic and her urine 0 255 mg These amounts are excessive and immediately raise the question as to the accuracy of her statement regarding treatment

Then ten cases of tertiary syphilitics included in Tables 4 and 5 gave the following analysis

TABLE 6—ARSENIC IN BLOOD AND URINE OF TEN TERTIARY SYPHILITICS

No	Arsenic in Blood, Mg	Arsenic in Urine, Mg	Source
1	None	0 744	Probably dietary
2	None	0 04	Probably dietary
3	0 03	0 16	Probably dietary
4	0 107	None	Probably dietary
5	0 069	0 024	Probably dietary
6	0 138	2 5	Probably arsenical medication
7	0 066	0 403	Probably dietary
8	0 8	18 5	This patient undoubtedly received arsenical treatment
9	0 9	0 009	Patient was on mixed diet, using large quantities of sweets and sugar daily
10	1 02	None	Probably dietary

TABLE 7—ARSENIC IN NORMAL BLOOD \*

A				B				
Patient Serial No	Weight of Specimen		Percentage Solids	Arsenic in Mg. per 100 Gm. of Dry Specimen	Diseases	Duration	Amount of Arsenic, Mg	Remarks
	Moist							
	Moist	Dry						
1935	2 5921	0 6375	25 68	Trace	Ache indurata	4 years	None	
1938	1 2473	1 2473	25 72	0 0400	Ache vulgaris	2 years	None	
1964	2 7822	0 5940	21 42	None	Ache vulgaris	3 years	None	
1960	1 4132	0 9145	20 58	None	Dermatophytosis	4 weeks	None	
1963	3 8308	0 7662	20 00	None	Dermatophytosis	1 year	None	
1939	5 6574	1 0935	19 33	None	Dermatophytosis	1 year	None	
1937	4 2954	0 9058	22 49	0 05	Dermatitis venenita	1 week	None	
1916	3 0083	0 7388	24 55	None	Eczema	6 years	None	
1954	3 8925	0 9546	24 52	None	Fpitheloma	8 years	None	
1977	2 6323	0 5652	21 30	None	Furunculosis	1½ years	None	
1901	2 8098	0 6314	22 70	None	Impetigo	1 week	None	
1953	3 8300	0 8121	21 21	None	Keloid	8 years	None	
1965	3 9855	0 9276	23 27	None	Leucoderma	2 months	None	
1944	3 7894	0 8173	21 56	None	Pruritis	2 weeks	None	
1915	3 4569	0 8392	24 31	0 474	Psoriasis	5 years	None	
1962	5 6276	1 4404	25 59	0 0694	Psoriasis	2 years	None	
1972	5 6127	1 3470	24 01	Trace	Psoriasis	18 years	None	
1939	3 4900	0 8152	23 35	None	Seborrhele dermatitis	7 years	None	
1933	4 4975	0 9014	20 31	0 220	Seborrhele dermatitis	1 month	None	
1955	3 2455	0 8336	27 53	None	Seborrhele dermatitis	4 years	None	
1941	2 3392	0 5160	22 05	None	Seabies	1 month	None	
1940	4 4848	1 3412	29 90	None	Syphilis, secondary	4 months	None	
1942	4 5032	1 0412	23 11	None	Syphilis, tertiary	Denied	None	
1943	4 1639	0 9945	23 87	None	Syphilis, tertiary	Denied	None	
1934	4 2633	1 1351	26 65	None	Syphilis (?)	Denied	None	
1936	5 6778	1 4574	25 66	None	Syphilis (?)	Denied	None	
1956	2 0444	0 4390	20 14	None	Syphilis (?)	Denied	None	
1952	3 9001	1 0780	27 64	None	Tinea profunda	5 months	None	
1958	2 9474	0 6849	23 57	None	Tinea circinata	1 week	None	
1951	4 8242	1 2089	25 03	None	Tinea versicolor	1 year	None	

2033	4 4812	0 9602	23 66	Trace	Tuberculosis verrucosa cutis	1 year	None
2050	4 0197	0 9049	22 51	0 5525	Urticaria	2 weeks	None
2060	4 4462	0 9836	22 12	0 3378	Urticaria	1 week	None
2062	4 0021	0 9924	21 56	None	Xanthoma	3 months	None
2033	2 8525	0 6623	23 22	None	Tinea	3 weeks	Trace
2039	3 6034	0 7910	21 60	0 2528	Tinea	2 weeks	Trace
2051	4 7224	0 7908	16 74	None	Leucoderma	8 months	Trace
2040	3 5645	0 7445	20 88	0 1343	Syphilis (?)	Denied	Trace
2047	1 4890	1 2329	27 46	None	Pott's disease	1 year	Trace
2042	1 0151	0 9037	22 50	0 0553	Alopecia areata	2 years	Trace
2043	3 3021	0 7895	23 09	None	Syphilis (?)	Denied	0 0397
2012	3 3823	0 8834	23 13	0 1698	Dermatitis venenata	6 months	0 04
2049	5 6073	1 4358	25 58	None	Scabies	2 weeks	0 05
2018	3 2715	0 6589	20 14	Trace	Syphilis (?)	Denied	0 0303
2059	5 7283	1 2587	21 97	0 0397	Folliculitis	7 years	0 0553
2011	4 4076	1 0403	23 60	0 0800	Dermatophytosis	3 months	0 0691
2015	4 3772	0 9932	22 69	0 0503	Syphilis (?)	Denied	0 080
2011	1 4041	0 9362	20 84	None	Alopecia	3 months	0 0962
2052	4 5131	1 0142	22 32	0 0986	Syphilis	Denied	0 1343
2078	3 7655	0 7663	20 41	None	Pruritis	1 week	0 1698
2001	3 4180	0 7304	21 18	None	Tinea cruris	1 year	0 220
2015	4 3155	1 0241	23 73	Trace	Impetigo	2 weeks	0 2528
2014	2 2985	0 5479	23 83	None	Eczema	Unknown	0 3378
2046	1 2705	1 0119	23 75	None	Sudamina	2 weeks	0 171
2014	2 2678	0 4315	19 02	Trace	Aene	5 years	0 5535

Location of above diseases Scalp, 2 ears, face, 11, neck, 2, chest, 2, trunk, 3, spine, 1, upper extremity, 6, hand, 9 lower extremity, 6, feet, 5, General, 8

\* Tables 7 and 8 contain the detailed analyses showing the disease, duration of disease, amount of arsenic found, with remarks as to the possible cause of the presence of arsenic. Findings in patients having no arsenic in their blood are arranged in that order in the second part of the table. For example, patient 194 had no arsenic in the blood, had aene indurata for four years, etc. Patient 1935 had time of three weeks' duration with only a trace of arsenic, probably of dietary origin. The results in portion A of each table are amplified by those in portion B in the order of magnitude in which the arsenic is found.

The patient with seborrhoeic dermatitis had 0.21 mg arsenic in the blood and none in the urine, the one with sycosis vulgaris was negative in both blood and urine, the case of alopecia areata showed a trace in the blood and 1.39 mg in the urine, chromophytosis, 0.306 mg in the blood and 0.067 mg in the urine, pityriasis rosea, 3.60 mg in the blood and 0.669 mg in the urine, and the patient with mucous cysts in the mouth had 2.12 mg in the blood and 0.15 mg in the urine. The last named was probably taking arsenic internally. In the case of pityriasis rosea the only explanation we could find was that of absorption from various ointments which the patient had applied locally. The source of the arsenic in alopecia areata and chromophytosis was either dietetic or medicinal.

The remaining two patients in this group came for a blood test. One was negative in both blood and urine, the other had 0.73 mg in his urine, his blood was lost, dietetics or medication would account for his excess.

*Normal Blood*—At the outset of this research we did not appreciate the difficulty of obtaining normal blood from absolutely normal persons. Our primary purpose was to obtain such specimens from groups of people, for example, in certain industries, but owing to lack of opportunity this procedure was not found feasible. Therefore, recourse was had to patients coming to the dermatologic department for minor affections of the skin. A special effort was made in the selection so that this series represents patients who came to the clinic for the first time and in whom we could exclude syphilis and, therefore, eliminate the possibility of their having received any arsenical medication.

Our analysis brought out the following facts: 55 cases, 41 men—32 white, 9 black, 14 women—10 white, 4 black. Ages ranged from 15 to 59 years. Occupations: none, 16, chauffeur, 2, sailor, 1, houseworker, 10, electrician, 1, waitress, 1, carpenter, 1, tailor, 5, laborer, 2, student, 3, shoemaker, 1, porter, 3, clerks, 4, teacher, 1, laundryman, 1, painter, 1, mechanic, 1, business man, 1.

*Normal Blood*—This group comprises clinic patients, most of them being old dermatologic cases, syphilitic cases who claimed they had had no previous treatment containing arsenic in any form and patients who came simply for a Wassermann examination of their blood.

Seventy-eight specimens were obtained from forty-one men—32 white and 9 black—and thirty-seven women—31 white and 6 black. Their ages ranged from 15 to 59 years. Their occupations were given as follows: None, 25, housework, 24, chauffeur, 1, waiter, 9, laborer, 1, furrier, 1, letter carrier, 1, printer, 1, collector, 1, sailor, 1, candy manufacturer, 1, student, 1, gelatin worker, 1, tailor, 5, shipping clerk, 1, office workers, 3, bookbinder, 1.

Location of diseases enumerated in Table 8 Face and head, 12, neck, 2, mouth, 2, chest, 4, trunk, 4, upper extremity, 2, hands, 4, lower extremity, 3, genitals, 2, eye, 3, nervous system, 1, general, 11, no external lesions, 28

The data in these cases are summarized in Table 8

In view of the fact that arsenic was present in so many of the cases under external or internal treatment, we can only assume that it was due to retention when ingested or absorption through the skin when applied locally Arsenic, as is well known, has a cumulative effect and many of these patients had been using these drugs over a long period In persons with a diseased skin, absorption is, of course, more active This has been illustrated a number of times in patients with epitheliomas who developed multiple neuritis after treatment with arsenical paste and died from arsenical poisoning

The tables show the composite results of analysis together with a chemical interpretation of each table In order to control these results the specimens were obtained under uniform conditions and analyzed as described in a preceding paper

Blood was obtained in sterile Wassermann tubes and weighed as soon as possible after being taken so that as much evaporation as possible was eliminated The percentage of solids was obtained by evaporation on the water bath and then in the hot air oven at 110 C to constant weight

The urine was collected by the patient with no control as to the amounts of liquid ingested The specimen was weighed as a liquid, then evaporated on the water bath and to constant weight in the hot air oven Specific gravity determinations were made at 25 C

In order to control the possibilities of arsenic contamination, the needles used for taking the blood were sterilized in the usual, routine manner The needles were then washed forcibly with a syringe and distilled water The water was analyzed for arsenic Four samples showed none, one sample contained a trace, three samples contained a half part, and one sample contained six parts These amounts were so small, with one exception, that they would in no way offer an explanation of any arsenic found in normal blood In Table 6 all the specimens analyzed were obtained by the use of thoroughly cleaned, new needles

Analysis of the rhubarb and soda mixture showed that it contained 0.0613 mg arsenic per hundred grams of drug The calamine lotion analyses were as follows solids, 17.09, 17.99, 16.58 and 18.12 per cent respectively, and the corresponding arsenic content per hundred grams



TABLE 8--ARSENIC IN NORMAL BLOOD

Patient Serial No	A		B		Remarks
	Weight of Specimen		Percentage Solids	Diseases	
	Moist	Dry			
1592	3.927	0.9062	23.17	1.41	Aene vulgaris
1590	3.8355	0.0371	24.08	Trace	Aene vulgaris
1593	7.3794	1.5074	20.45	1.99	Aphthous stomatitis
1610	6.0826	1.3132	21.58	0.1761	Bazin's disease
1598	5.0973	1.0388	20.77	None	Carcinoma breast
1491	5.1097	1.1635	22.76	None	Eczema
1643	4.8236	1.1080	22.97	None	Eczema
1408	4.7397	1.0180	21.47	0.530	Epithelioma
1101	7.0233	1.1019	23.99	None	Iritis
1608	4.5919	1.3015	23.33	None	Leprosy
1193	5.5765	0.9566	26.31	0.0132	Onychomycosis
1616	3.6318	0.9566	24.60	0.12	Sebaceous cyst
1650	6.7250	1.6555	20.300	0.780	Syphilis (?)
1637	4.7328	0.9608	21.06	0.873	Syphilis (?)
1581	4.5324	0.9548	22.77	None	Syphilis (?)
1576	4.8441	0.9040	30.11	0.033	Syphilis, secondary
1494	5.5309	2.2673	21.61	Trace	Syphilis, secondary
1603	5.5355	1.1983	22.69	None	Syphilis, tertiary
1106	5.292	1.2010	19.56	1.92	Syphilis, tertiary
1532	5.3238	1.0415	23.79	None	Syphilis, tertiary
1545	4.5911	1.0923	21.43	None	Syphilis, tertiary
1582	4.4355	0.9506	21.43	None	Syphilis, tertiary
1530	4.3169	0.9941	23.02	0.1005	Syphilis, tertiary
1602	5.4417	1.0615	19.50	None	Syphilis, tertiary
1584	3.6601	0.7335	20.04	1.36	Syphilis, tertiary
1641	4.6493	1.0217	21.97	0.244	Syphilis, tertiary
1543	6.2327	1.2850	20.42	0.259	Syphilis, tertiary
1663	6.2400	1.6750	26.84	None	Tabes
1587	8.2021	2.3845	25.33	5.24	Chancroid
1518	6.2000	1.5708	25.33	None	Tertiary syphilis
1595	4.4510	0.8900	19.99	0.1561	Occupational dermatitis
1642	5.6875	1.2692	22.15	0.396	Congenital syphilis
1620	4.0569	1.0143	22.26	None	Lupus vulgaris
1594	5.6870	1.3312	23.40	1.001	Tertiary syphilis
1588	6.5015	1.3809	21.23	30.1	Hydrocele
1570	5.0793	1.1268	22.10	2.67	Aene eacheetecorum
1283	4.2035	0.9642	22.94	0.051	Tertiary syphilis
1489	5.0408	1.1079	21.97	0.225	Pruritis
1596	5.4645	1.2449	22.78	0.0548	Optic atrophy

1544	3 6871	0 7849	21 28	None	None	Syphilis (?)	Denied	0 14	Medication
1541	4 9726	1 0779	21 69	0 0652	0 301	Tertiary syphilis	Denied	0 1005	Medication
1172	5 9667	1 4437	24 44	0 017	0 069	Scorbutic dermatitis	30 years	0 105	Using ungt sulphur
1578	41 5774	0 9074	23 90	0 132	0 551	Tertiary syphilis	6 years	0 1561	Medication
1173	5 1458	1 0635	20 67	0 00961	0 047	Pruritis	2 weeks	0 16	Medication
1638	6 5644	1 5514	22 70	0 0152	0 0614	Tertiary syphilis	5 years	0 17	Medication
1600	5 9534	1 3016	21 86	0 0163	0 0769	Acne vulgaris	1 year	0 1761	Using lotio alba and R & S
1606	5 2574	1 1914	22 66	0 190	0 840	Tertiary syphilis	Denied	0 196	Medication
1539	5 2966	1 2385	23 42	0 141	0 605	Tertiary syphilis	Denied	0 225	Also had herpes zoster, probably arsenical
1645	4 1525	0 9859	23 74	None	None	Acne vulgaris	1½ years	0 241	Using lotio alba and R & S
1531	1 0764	0 9718	23 83	0 0122	0 0514	Pruritis	15 years	0 250	Using lotio alba and calamine and zinc lotion
1515	5 0366	1 2070	23 96	0 0397	0 16	Secondary syphilis	6 months	0 259	Medication
1190	5 2260	1 3081	25 05	None	None	Ititis	Unknown	0 259	Medication
1639	5 3136	1 2134	23 96	0 0188	0 0824	Syphilis	Denied	0 301	Medication
1319	5 5749	1 2142	21 77	None	None	Urticaria	9 weeks	0 306	Using lotio alba, calamine and zinc, and R & S
1538	1 2039	0 9498	22 59	0 0237	0 105	Rosacea	6 months	0 479	Using lotio alba and R & S
1192	5 7100	1 0623	18 506	0 298	1 61	Rosacea	6 years	0 514	Medication
1599	6 3467	1 6012	23 66	0 0473	0 250	Epitheliom 1	6 months	0 51	Probably medication
1607	5 4657	1 1533	21 10	None	None	Celiditis	1 month	0 651	Using ungt ichthyol
1580	1 6539	1 3945	23 96	0 143	0 479	Scabies	3 months	0 665	Using ungt sulphur
1601	1 4935	1 0241	22 78	None	None	Pityriasis rosea 1	1 week	0 704	Using lotio alba, calamine and zinc, and R & S
1317	5 7105	1 1410	21 76	0 035	0 14	Secondary syphilis	5 months	0 717	Medication
1597	4 8997	1 1462	23 39	0 272	1 16	Congenital syphilis	23 years	0 78	Medication
1517	6 8070	1 5250	22 40	0 044	0 196	Secondary syphilis	3 months	0 824	Medication
1589	5 4973	1 1188	20 90	0 102	0 187	Tertiary syphilis	10 years	0 84	Undoubtedly medication
1607	5 3835	1 2285	22 82	0 162	0 717	Ulcer tongue	2 years	0 873	Medication
1577	3 7865	0 8725	22 52	0 168	0 704	Tertiary syphilis	Unknown	1 001	Undoubtedly medication
1583	6 9960	1 6412	23 46	0 428	1 82	Tertiary syphilis	Unknown	1 16	Undoubtedly medication
1585	1 4125	0 9182	20 66	1 35	6 53	Tertiary syphilis	Unknown	1 36	Undoubtedly medication
1601	5 2316	1 1311	21 62	None	None	Tertiary syphilis	10 years	1 69	Undoubtedly medication
1591	5 0270	1 0763	21 02	None	None	Secondary syphilis	6 months	1 61	Undoubtedly medication
1590	1 1708	0 8440	20 23	None	None	Acne vulgaris	1 year	1 82	Undoubtedly medication
1239	5 7706	1 2483	21 80	0 0175	0 087	Congenital syphilis	25 years	1 92	Undoubtedly medication
1516	6 0045	1 4511	21 16	0 385	1 069	Acne vulgaris	6 months	1 99	Undoubtedly medication
1487	5 7156	0 6774	01 004	None	None	Acne vulgaris	6 months	2 67	Undoubtedly medication
1517	1 5900	1 6311	22 899	Trace	Trace	Herpes zoster	2 weeks	4 41	Undoubtedly medication
1510	0 2463	1 3457	21 22	None	None	Tertiary syphilis	Unknown	5 21	Undoubtedly medication
1641	1 8772	1 0622	21 17	None	None	Tertiary syphilis	5 years	6 3	Undoubtedly medication
1642	6 1837	1 1914	21 22	None	None	Tertiary syphilis	20 years	9 1	Undoubtedly medication

was 0.4929, 0.7742, 0.8051, and 0.7774 mg metallic arsenic, respectively. The variations are probably due to different degrees of suspension.

Sulphur ointments showed one sample with a trace of arsenic and the other with 0.3141 mg arsenic per hundred grams. Analyses of lotio alba showed that arsenic in amounts of 0.361 and 0.561 mg was found in specimens which were being used in the clinic. Ichthyol also contained arsenic to the extent of 0.334 mg per hundred grams of drug.

#### SUMMARY

As a result of the examination of the blood, urine, hair and milk from about 200 subjects we can conservatively state that arsenic is found "normally" in a large number of persons, depending on the character of their food, drink, medication and environment. It is absent in persons on a diet restricted in the amount of sweets, vegetables, meat, etc., and it is present in varying amounts in persons applying remedies containing ingredients contaminated with arsenic to inflamed or ulcerating skin surfaces, and to a greater extent in persons receiving arsenic either by mouth or intravenously or connected with the arsenicals in a preparative way.

"Normal" is interpreted as meaning the result found when a large number of persons are examined. Tables 1 to 7 show that it is not necessary for every person to show a positive test at all times. These tables show to some extent that all drugs and foods are contributing factors in the detection of arsenic in human beings, depending, of course, on the method of manufacture and the preparation of the food. Arsenic is also secreted in the milk and is found in hair and skin tissue.

It was difficult to obtain specimens from a large number of normal persons in whom we could control absolutely the character of their diet. In the few who could be relied on the analyses showed quite definitely the absence of the drug where an arsenic-free diet had been carried out. Most of our specimens were from patients with the various common skin diseases such as eczema, urticaria, psoriasis, acne, etc. In some of these patients disordered metabolism is a contributing factor and a possible cause for the variations in the amounts of arsenic found.

Consideration of the results in the tables shows that a complete history of the subject is necessary before arriving at a decision regarding the arsenic content of the urine, blood or even of the organs. In the determination of the amount found "normally" in the body fluids the ideal way would be to hospitalize the subject in order to regulate the nature and amount of food ingested and to check up false statements regarding medication. Consideration of the "normal" arsenic is necessary from a medicolegal point of view. This investigation shows that

it may be a normal constituent of the body under the conditions studied and that excessive amounts should always be considered with suspicion in patients who present themselves for examination and medication <sup>21</sup>

21 The following references also bear on this subject

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- Effront, J Acquired Tolerance of Beer Yeast for Arsenic, Mechanism of the Acquired Tolerance of Micro-Organisms for Toxic Substances *Reunion soc belge biol*, 1920, p 99, *Physiol Abstr* **5** 437, 1920
- Gautier, A Localisation, elimination, et origines de l'arsenic chez les animaux, *Compt rend* **130** 284, 1900 La fonction mnstrucelle et le rut des animaux Rôle de l'arsenic dans l'economie, *Compt rend* **131** 361 1900 L'arsenic existe normalement chez les animaux et se localise surtout dans leurs organes ectodermiques, *Compt rend* **134** 1394, 1902 A propos de la Note de M G Bertrand, presente les observations suivantes, *Compt rend* **135** 812, 1902
- Foreign Letters Hydrogen Arsenic Poisoning in Submarines, *J A M A* **73** 1148 (Oct 11) 1919 Government Control of Antisyphilitic Arsenicals, *J A M A* **78** 595 (Feb 28) 1922
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- Niven, J Report to the Hospitals Subcommittee of the Manchester Sanitary Committee of the Outbreak of Arsenical Poisoning Now in Progress in Manchester, *Lancet* **2** 1752, 1900 The Beer Poisoning Epidemic, *Lancet* **1** 570, 1901
- Shattuck, F C Some Remarks on Arsenical Poisoning with Special Reference to Its Domestic Sources, *Med News* **62** 589, 1893

# URICACIDEMIA

BASED ON A STUDY OF 1,500 BLOOD CHEMICAL ANALYSES \*

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Research in blood chemistry and its clinical application has been almost entirely an American achievement. When it is recalled that this whole subject is now only in its infancy, the widespread use of blood chemical analyses is quite remarkable. Ten years ago accurate clinical methods for the determination of blood urea, uric acid, and creatinin were practically unknown. Closely following the invention of suitable technical procedure, many conclusions have been stated and reiterated as to the significance of high blood concentration of these substances. Some of them are based on slow, painstaking scientific work, others are largely the result of ingenious surmises supported by cases selected to prove the point.

This paper deals with the interpretation of high uric acid figures in the blood. Before 1912 there had been practically no work on this theme. The fact that in gout there was an excess of uric acid in the blood, which could be revealed by Garrod's string test, just about comprised our knowledge at that time.

Folin and Denis,<sup>1</sup> in 1912, opened this whole field when they described a convenient and accurate method for the determination of the uric acid of the blood. Later they observed that in gout, lead poisoning and leukemia, high blood concentration figures are apt to be found. They<sup>2</sup> emphasized the absence of relationship between the amount of uric acid and that of total nonprotein nitrogen (or urea nitrogen) in the blood.

An analysis made by me<sup>3</sup> of twenty-nine cases of uremia showed this lack of parallelism very strikingly. Thus two patients, each with 375 mg of urea nitrogen per 100 c c, gave uric acid readings of 35.7 and 5, respectively. In that series, uric acid was invariably increased, but there was an absence of proportion in the retention figures.

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\* From the Clinical Laboratory, Department of Internal Medicine, Long Island College Hospital.

1 Folin, O, and Denis, W. A New (Colorimetric) Method for the Determination of Uric Acid in Blood, *J Biol Chem* **13** 469 (Nov. 30) 1912.

2 Folin, O, and Denis, W. Protein Metabolism from the Standpoint of Blood and Tissue Analysis, *J Biol Chem* **14** 29, 1913.

3 Feinblatt, H. M. Uremia. An Analysis of Twenty-Nine Cases, New York M. J., awaiting publication.

Folin and Denis<sup>4</sup> in 1915 stressed the necessity of correlating all uric acid readings with those of the total nonprotein nitrogen (or urea nitrogen). They divided bloods into four classes: (1) those with retention of uric acid alone, (2) those with retention of the total nonprotein nitrogen but not of uric acid, (3) those with retention of both, and (4) those with retention of neither. They pointed out that in gout the uric acid alone is apt to be increased, while in nongouty arthritis both substances are usually retained.

The capriciousness of uric acid was later noted by Pratt<sup>5</sup> in his studies on gout. In sixteen gouty patients he found no relation between the degree of retention of uric acid and the severity of the symptoms, and in two subjects with marked uratic tophi the blood values were within normal limits.

Myers, Fine and Lough<sup>6</sup> were impressed with the value of uric acid retention as an early sign of chronic interstitial nephritis. They reported thirty selected cases with high uric acid figures and no, or only moderate, retention of urea, which appeared to be cases of early chronic interstitial nephritis.

Chace and Myers<sup>7</sup> stated their opinion as follows: "An increase in the uric acid of the blood would appear to be of considerable value as an early diagnostic sign of incipient nephritis." In their tables most of the cases showed concurrent retention of urea, some even of creatinin. They certainly could not be considered as instances of specific retention of uric acid. Furthermore, the use of selected cases instead of routine series greatly limits the value of the work as a scientific contribution.

The questions immediately arise. Granted that uric acid retention may occur in early chronic interstitial nephritis, how uniformly does this happen? Is retention of uric acid peculiar to chronic interstitial nephritis, or, if it does occur in other conditions, can the latter be differentiated readily? These questions must be answered definitely before one can safely interpret uricacidemia as an evidence of nephritis.

Baumann<sup>8</sup> and others, in 1919, reported high uric acid readings in 74 per cent of 100 cases of early nephritis. The study was largely

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4 Folin, O., and Denis, W. The Diagnostic Value of Uric Acid Determination in Blood, *Arch Int Med* **16** 33 (July) 1915.

5 Pratt, J. H. The Uric Acid in Blood in Gout, *Am J M Sc* **151** 92 (Jan) 1916.

6 Myers, V. C., Fine, M. S., and Lough, W. G. The Significance of the Uric Acid, Urea and Creatinin of the Blood in Nephritis, *Arch Int Med* **17** 570 (April) 1916.

7 Chace, A. F., and Myers, V. C. The Value of Recent Laboratory Tests in the Diagnosis and Treatment of Nephritis, *J A M A* **67** 929 (Sept 23) 1916.

8 Baumann, L., Hansmann, G. H., Davis, A. C., and Stevens, F. A. The Uric Acid Content of Blood Compared with the Renal Dietary Test, *Arch Int Med* **24** 70 (July) 1919.

TABLE 1

Name	Age	Sex*	Blood Chemistry				Diagnosis	Outcome	Complications	Evidences of nephritis
			Urea			Sugar				
			Uric Acid	N	Creat- Inin					
D A O K	42 12	♀ ♂	12.5 8.3	15 20	1.5 2	105 80	Hyperemesis gravidarum Chronic glomerular nephritis	D I	Chronic myocarditis	None Hypertension, albumin, casts, reti- nal hemorrhages and optic neur- itis, phenolsulphonethalein, 33 per cent None None None
A M J D P L	37 20 43	♂ ♂ ♂	8.2 7.13 7.13	9 11.5 10.7	1.3 1.5 1.67	95 87 100	Duodenal ulcer Illuminating gas poisoning Heated duodenal ulcer, with hour glass constriction Benign hypertension Lethargic encephalitis	I D I	Secondary anemia Bronchopneumonia Constipation	None None None
I G M W	63 43	♀ ♂	6.2 6 3.8	12 9.6 12	1.3 1.5 1.75	133 117.6 105	Aortic and mitral regurgitation, rheumatic Lacerations of cervix and peri- neum Influenza and bronchopneu- monia	I I	Hypertrophied tonsils Secondary anemia Pregnancy	Blood pressure 240/110 Blood pressure 130/120, trace of albumin, hyaline and granular casts None
W R H W	13 25	♂ ♀	6 5.5	15 12	1.4 1.5	100 95	Aortic and mitral regurgitation, rheumatic Lacerations of cervix and peri- neum Influenza and bronchopneu- monia	I I	Hypertrophied tonsils Secondary anemia Pregnancy	None None None
P S L L L N M B I B	35 63 64 72 53	♀ ♂ ♂ ♂ ♀	5 5 5 5 5	10 12 15 13 13	1.3 1.67 1.4 1.5 1.5	100 90 100 333 83	Adenoma of prostate Chronic cholecystitis Illuminating gas poisoning Lethargic encephalitis	R I I I I	Syphilis	None None None Blood pressure 155/95, few hyaline casts None
M A L H P F	47 21 62	♀ ♂ ♂	5 4.53 4.53	12.75 8.6 15	1.35 1.67 1.36	100 87 105	Cerebral thrombosis, syphilitic Traumatic synovitis (knee) Hyperpituitarism	D I I	Arteriosclerosis, diverticu- lum of urinary bladder Hypernephrosis, myositis Periosteal adhesions Pregnancy	None Blood pressure 150/75 None None Pylonephrosis
C L W F B F	35 36 30	♂ ♂ ♀	4.53 4.53 4.53	17.6 12 12.5	1.5 1.5 1.53	80 100 77	Chronic cholecystitis Chronic appendicitis Intermittent pyelonephrosis, one kidney absent	I I R	Hypernephrosis, myositis Periosteal adhesions Pregnancy	None None Pylonephrosis
K M M H	16 32	♂ ♂	4.5 4.5	13.6 10	1.7 1.5	75 109	Cellulitis of arm (Streptococcus hemolyticus) Oral sepsis	R R	Constipation	None None

L G	40	♂	4.4	16.6	1.5	111	Neurasthenia	U	Retention of urine	None
T H	60	♂	4.2	17.6	2	110	Hypertrophied prostate	I	Secondary anemia, possible	None
A C	49	♂	4.2	13.4	1.3	109	Cerebral hemorrhage	I	Chronic glomerular nephritis	Hypertension, casts, albumin
W H	51	♂	1.2	17	1.6	125	Benign hypertension	I	Aortic stenosis	Blood pressure 160/110, albumin, specific gravity 1.012-1.022
M B	50	♀	4.2	12	1.4	200	Lobar pneumonia	R	Mitral regurgitation	Blood pressure 160/80, casts, trace of albumin
J A	41	♀	4.2	15	1.5	80	Multiple arthritis	I	Hypertrophied tonsils	Blood pressure 165/105
S C	25	♂	4.15	13.6	1.5	100	Bell's palsy	I	Chronic colitis, possible	None
M S	46	♀	1.15	10	1.67	111	Benign hypertension, arterio sclerosis	I	early nephritis	Blood pressure 190/120, azotemic casts, phenolsulphonate, thalein, 40 per cent
V C	64	♀	4.15	10	1.5	181	Arteriosclerotic kidney	I	Fibrositis, knee, possible early nephritis	Blood pressure 218/85, phenolsulphonate, 50 per cent, specific gravity, 1.011-1.020, night urine, 710 cc, day urine, 735 cc, hyaline and granular casts
A S	33	♂	4.15	17.6	1.43	90	Tertian malaria	R	Tertiary syphilis	None
J K	41	♂	4.1	15	1.8	143	Chronic cholecystitis	I	Secondary anemia	None
L K	32	♂	4.1	12	1.3	111	Hemorrhoids	I	Secondary anemia	None
H H	56	♂	4.1	15	1.5	133	Cerebral concussion	R	Pulmonary tuberculosis, pleurisy	None
P I	41	♂	4.1	12	1.5	125	Pott's disease	I	Menopause	None
T S	49	♀	3.83	15	1.36	100	Benign hypertension	I		Blood pressure 190/110, phenolsulphonate, 57 per cent, specific gravity, 1.000-1.025, night urine, 220 cc, day urine, 1020 cc
R T	18	♂	3.83	15	1.5	105	Acute bronchitis	R		None
O M	30	♂	3.83	8.3	1.5	333	Typhoid fever	R	Albumin, few granular casts	None
M T	26	♂	3.8	20	1.5	125	Acute follicular tonsillitis	R		None
F V	18	♀	3.8	19	1.3	100	Idiopathic epilepsy	I		None
I L	20	♀	3.8	9	1.4	125	Chronic cholecystitis	I		None
R K	39	♂	3.6	15	1.6	100	Cerebral thrombosis	I	Tonsillitis, otitis media	None
J V	45	♀	3.55	13.6	1.5	181	Essential hematuria	I		Albumin hematuria, phenolsulphonate, 60 per cent, specific gravity, 1.012-1.016
I V	31	♀	3.5	15	1.6	133	Urticaria	I		None
J J	27	♀	3.5	12	2	111	Chronic glomerular nephritis	I		Blood pressure 245/165 albumin, specific gravity 1.010-1.018
C S	60	♀	3.5	16.7	1.5	333	Hypernephroma, right kidney	R		Blood pressure 160/80, trace of albumin

\* In this column, ♂ indicates male, and ♀ female



limited to instances of nephritis and arteriosclerosis. High urea figures were frequently associated.

The obstetrician has utilized uric acid determinations for diagnostic purposes. Williams,<sup>9</sup> in 1921, demonstrated that in eclampsia, pre-eclamptic toxemia, and toxic hyperemesis gravidarum, retention of only uric acid is the rule. With delivery and recovery from the symptoms the blood value returns to normal.

Chauffard<sup>10</sup> attributes a common origin to gout and nephrolithiasis. He found uric acid retention to be the rule in both conditions. In three dogs he obtained much higher uric acid readings from the portal vein than from the peripheral veins. He ascribes uricacidemia principally to a loss of the uricolytic function of the liver.

Perroncito<sup>11</sup> likewise showed that after removal of the liver the blood uric acid rapidly rose while the urea values fell abruptly. These observations would suggest that uric acid is not very readily eliminated even by the undamaged kidney and that high blood concentration often results from diminution of the uricolytic function of the liver.

#### TECHNIC

The blood was drawn before breakfast on the day following that of admission. These patients were not kept on a purin free diet. At one time it was considered essential to make the determination only after the patient had been subjected to a purin free diet for a period of two weeks. Denis'<sup>12</sup> studies showed that this is not necessary. She observed that in normal men there is no increase in the blood uric acid values even after the ingestion of large amounts of purins.

The technic employed was that of Folin<sup>13</sup>

#### MATERIAL STUDIED

Out of 1,500 blood chemical analyses taken in the wards of the Long Island College Hospital, there were separated all of those cases, regardless of diagnosis, which conformed to the following specifications: Uric acid, 3.5 mg per 100 c.c. or more, urea nitrogen, 20 mg per 100 c.c. or less, creatinin, 2 mg per 100 c.c. or less. Blood chemical analyses were made in medical cases as a matter of routine. This scheme of mechanical winnowing must obviously yield results which are entirely

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9 Williams, J. L. Increased Amount of Uric Acid in Blood in Toxemias of Pregnancy, *J. A. M. A.* **76** 1297 (May 7) 1921.

10 Chauffard, A. Brodin, P., and Grigaut, A. L'Hyperuricémie dans la Goutte et dans la Gravelle, *Presse med.* **28** 905 (Dec 15) 1920.

11 Perroncito, A. Extirpation of liver, *Riforma med.* **36** 830 (Sept 11) 1920.

12 Denis, W. Effect of Ingested Purins on Uric Acid Content of Blood, *J. Biol. Chem.* **23** 147 (Nov) 1915.

13 Folin, O. A Laboratory Manual of Biological Chemistry, 1919, p. 193.

free from prejudices. Because of the large number of cases considered, the findings may be considered as fairly representative, subject, of course, to any special types of patients treated at this institution<sup>14</sup>. There was no selection of cases. This system of mechanical winnowing was utilized in the study of creatinemia<sup>15</sup> which condition, thus investigated, proved to be associated with grave renal insufficiency in 100 per cent of instances.

The data on all of the uricacidemic patients are tabulated in Table 1.

Out of 1,500 routine analyses, forty-seven patients exhibited uricacidemia without concurrent retention of urea or creatinin. From a glance at Table 1 it becomes apparent that this finding may be present in many and varied conditions.

Table 2 summarizes the diagnosis in these forty-seven cases.

TABLE 2—SUMMARY OF CLINICAL DIAGNOSES IN FORTY-SEVEN URICACIDEMIC SUBJECTS

Diagnosis	No. Cases
Benign hypertension	5
Chronic cholecystitis	4
Duodenal ulcer	2
Chronic glomerular nephritis	2
Illuminating gas poisoning	2
Lethargic encephalitis	2
Cerebral thrombosis	2
Miscellaneous conditions (occurring only once)	28

Because of the often expressed view that uric acid retention is to be considered as an evidence of nephritis, this series of cases was studied with especial care as to other signs of renal lesions. The urine, the renal test meal, the phenolsulphonephthalein test, the blood pressure and the eyegrounds were among the other avenues of approach. Thus studied, two of the cases were diagnosed as chronic glomerular nephritis, five as benign hypertension (probably associated with arteriosclerosis of the vasa afferentia to the renal glomeruli), and one as pyelonephrosis. The remaining thirty-nine cases were not considered as belonging to the kidney group.

Altogether, thirty of the forty-seven patients revealed none of the signs of renal disease, although these were systematically looked for. In seventeen cases there were present some of the evidences pointing to the kidney, but in nine of these the evidence was considered insufficient to justify the diagnosis of a nephropathy.

The multiplicity of conditions in which uricacidemia may eventuate should indicate that this finding must be interpreted with considerable

14 The cases treated at the Long Island College Hospital are fairly representative in type.

15 Feinblatt, H. M. Creatinemia Based upon a Study of 1,500 Blood Chemical Analyses, Am J M Sc, awaiting publication.

caution To base a diagnosis of chronic interstitial nephritis merely on uric acid retention appears to be altogether unwarranted

In a recent Harvey lecture, Folin<sup>16</sup> took a very conservative stand on the subject of uricacidemia He said

A very important point yet to be solved is the question whether the kidneys are or are not selective with reference to the excretion of the nitrogenous waste products Are the kidneys of those who have or are going to have gout damaged specifically with reference to their power of eliminating uric acid? That is too fundamental a problem to permit any ill founded dogmatism It certainly is true that in those who have gout one is likely to find abnormally high uric acid accompanied by a perfectly normal level for all the other nitrogenous constituents Whereas, in nephritis we may have very high levels of nitrogen retention and substantially normal uric acid values I hesitate to say anything very definite on this whole question

Two facts invalidate uric acid as an index to renal efficiency viz, the frequent occurrence of retention in totally unrelated conditions and the often observed lack of parallelism with urea and creatinin in known cases of nephritis

It is by no means rare in uremia, while the patient is comatose and the creatinin and urea nitrogen figures are rising, to note a marked drop in the blood uric acid figure Three such instances are described below in Table 3

TABLE 3—SUDDEN DROP IN URIC ACID CONCENTRATION IN THREE FATAL CASES OF UREMIA

Name	Age	Sex§	Date of Analysis	Uric Acid	Urea N	Creatinin	Sugar	Date of Death
V H *	25	♂	2/17/20	6.2	50	7.5	133.8	2/28/20
			2/21/20	12.5	300	8.6	200	
			2/24/20	8.2	300	15	143	
			2/27/20	5	375	20	138	
H G †	43	♀	3/26/21	8.33	50	3.75	166	4/ 5/21
			3/29/21	4.15	60	4.28	111	
H A ‡	29	♀	2/17/19	10	100	6.5	142	2/21/19
			2/19/19	4.3	115	6.6	200	

\* Acute exacerbation of chronic glomerular nephritis Patient was uremic and died in coma

† Acute exacerbation of chronic glomerular nephritis, confirmed by necropsy

‡ Congestive necrosis of renal tubules due to mercuric chlorid poisoning, complicated by gangrenous stomatitis and gastro-enteritis Confirmed by necropsy

§ In this column, ♂ signifies male, ♀ female

In uremia a certain rough ratio can be detected between the urea nitrogen and the creatinin figures They rise together as death approaches and descend proportionately with improvement No such parallel exists in the case of uric acid The data recorded in Table 3 are irreconcilable with the view that uricacidemia is a sensitive test of slight degrees of renal inefficiency

It is not my purpose to attempt to annihilate all interpretations placed on high blood uric acid concentration. The common finding of uricacidemia, without retention of total nonprotein nitrogen, in gout, nephrolithiasis, leukemia, lead poisoning, hyperemesis gravidarum and eclampsia, has been abundantly shown. However, it should be stressed that this state may also obtain in a vast number of unrelated conditions, under circumstances which are not yet understood. The blood uric acid, therefore, cannot be considered in any sense as diagnostic but should be thought of as a symptom. Given an arthritis of the small joints, uricacidemia furnishes an additional sign in favor of gout, or, in a case of hyperemesis gravidarum a high uric acid reading indicates that the condition is toxic rather than neurotic. Any effort to assign to uricacidemia a uniform interpretation, *i. e.*, chronic interstitial nephritis, is an assumption not warranted by known facts.

#### CONCLUSIONS

1 Uricacidemia may occur in a large number of totally unrelated conditions.

2 A study of 1,500 persons with routine blood chemical analyses showed that the great majority of patients with high blood concentration of uric acid but not of urea nitrogen or creatinin exhibited no evidence at all of early chronic interstitial nephritis.

3 In uremia there is a lack of parallelism between the figures for uric acid, on the one hand, and those for urea nitrogen and creatinin on the other. Frequently, with mounting urea nitrogen and creatinin, and deepening coma, terminating in death, the concentration of uric acid in the blood takes a marked drop. There is often but slight retention of uric acid in moribund uremics.

4 The blood uric acid reading is of no value unless correlated with that of urea nitrogen (or total nonprotein nitrogen). A high concentration may be interpreted as a symptom, along with the other manifestations, but is in no sense diagnostic in itself of early chronic interstitial nephritis or any other condition.

# ACCURATE CRITERIA FOR DIFFERENTIATING ANEMIAS <sup>†</sup>

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In differentiating types of anemia, clinicians are constantly making use of the relationship between the number of erythrocytes and the hemoglobin. This relationship is usually expressed as the color index. In view of its wide use, it is surprising how vague are the ideas of the factors on which the color index is fundamentally based. This is due, in some measure, to the common use of only relative methods for the determination of hemoglobin. To arrive at precise information, it is necessary to have the hemoglobin content expressed in exact terms of grams per hundred cubic centimeters. Suggestions for a normal hemoglobin standard on this basis have been pointed out elsewhere <sup>1</sup>

Very few careful studies of color index have been made. It is not even universally agreed that the color index of normal blood is always 1.00. Meyer and Butterfield,<sup>2</sup> on the basis of a very few observations with hemoglobin determinations by the spectroscopic method, conclude that such is always true.

A proper understanding of the relationship between hemoglobin and erythrocytes presupposes a knowledge of the number, the size and the hemoglobin content of the red cells. It is commonly thought that color index is an expression indicating the percentage of hemoglobin in the cells. This is true only when the cells are of normal volume. The index in reality depends on both the size and the hemoglobin content. As ordinarily determined, the size of the cell is not taken into consideration.

In 1903 Capps<sup>3</sup> emphasized the value of the study of the size of the erythrocyte. He introduced the term "volume index" to express the volume of the red cell as compared with the normal. Since that time little use has been made of the index. Only two articles concerning it have appeared in the literature. Capps determined the volume of the red cells with Daland's hematocrit, which is relatively crude and gives no information on which the exact volume of the average cell may be calculated. His hemoglobin determination was made by a relative

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\*From the Department of Medicine, University of Kansas, School of Medicine.

1 Haden, R. L. J. A. M. A. 79:1496 (Oct. 28) 1922.

2 Meyer, Erick and Butterfield, E. E. Arch. Int. Med. 14:94 (July) 1914.

3 Capps, J. A. J. M. Research 5:367, 1903.

method, namely, that of von Fleischl, the results of which cannot be translated into grams or be made the basis for calculating the hemoglobin content of the average red cell

Capps emphasized that in pernicious anemia the volume of the average cell is greater than normal, and that in secondary anemia it is smaller. In pernicious anemia he found the color index greater than the volume index. The importance of this will be pointed out later. He did find a volume index greater than 1.00 in conditions other than pernicious anemia, however. He did not calculate in any instance the actual volume and hemoglobin content of the average cell. Wroth<sup>4</sup> reports a few cases which confirm Capps' conclusions. Larrabee,<sup>5</sup> working with a slightly different technic, did not have such constant results.

It is certainly true that few clinicians ever make use of the volume index. In some of the most recent discussions of anemia no mention is even made of its value and use in differential diagnosis in certain types of anemia.

In connection with a study of blood volume, Hooper, Smith, Belt and Whipple<sup>6</sup> have recently suggested a method for the accurate determination of the volume of the mass of red cells. A relatively large quantity of blood (10 c c) is taken, and an anticoagulant isotonic with the blood is used, thus preventing any shrinking or swelling of the cells. Much more constant and exact results are obtained than is possible with either the hematocrit of Daland or by adding an indefinite quantity of solid potassium oxalate directly to the blood. From the data obtained, together with the counts, the exact volume of the average cell may be calculated. Likewise there is now available for hemoglobin estimation the very exact oxygen capacity method of Haldane<sup>7</sup> as adapted by Van Slyke<sup>8</sup> to his blood gas apparatus. The results are expressed in grams per hundred cubic centimeters.

I have employed these two precise methods in a study of the blood of a large number of normal persons and in anemia of different types. The volume and color index have been calculated for each blood examined. Since the color index does not express the amount of hemoglobin per unit volume of cell, I have calculated a new index which does express this value. This index I have called the "saturation index" to indicate that it shows the relative amount of hemoglobin in the red cells as compared with the normal. Only in normal blood is it

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4 Wroth, P. *Bull Johns Hopkins Hosp* **18** 59, 1907

5 Larrabee, R. C. *J M Research* **24** 15, 1911

6 Hooper, Smith, Belt and Whipple. *Am J Physiol* **51** 205, 1920

7 Haldane, J. S. *J Physiol* **22** 298, 1898

8 Van Slyke, D. D. *J Biol Chem* **33** 31, 1918

synonymous with the color index. The saturation index shows the same relation of the hemoglobin to the cell as the volume index does of the volume. The color index depends on these two indices.

From the data obtained on the absolute volume of the red cells and the hemoglobin I have calculated the exact volume and the exact hemoglobin content of the average red cell in each blood examined, and in turn the exact percentage of hemoglobin in the red cells.

#### METHODS

All determinations have been made on venous blood. The following procedure has been followed: 20 c.c. of blood is withdrawn by venipuncture, 10 c.c. of which is immediately run into a 15 c.c. graduated centrifuge tube containing 2 c.c. of 16 per cent sodium oxalate solution and mixed by inversion. The tube is then centrifuged for thirty minutes at 2,500 revolutions per minute and the volume of packed red cells read off. The remaining blood is run into a test tube or flask containing 40 mg. of potassium oxalate and mixed thoroughly. From this oxalated specimen two red cell pipets are filled in the usual manner for counting. The tube or flask is then rotated for five minutes in such a manner as to keep the blood in a thin layer on the sides of the container. The hemoglobin is thus completely converted into oxyhemoglobin. Duplicate hemoglobin determinations are made with the Van Slyke apparatus. The determinations have been made by both the original technic<sup>8</sup> and by the revised method<sup>9</sup>. Identical results have been obtained with the two methods. Van Slyke has shown that the calculation as originally given is incorrect since sufficient allowance was not made for the nitrogen content of the blood. I have made all calculations by the revised method.

In determining the volume of the cells, two centrifuges have been used at different times. The more powerful centrifuge gave slightly better packing (46 per cent of cells per 5 million cells). All volume results have been figured on this basis. It should be emphasized here that in making volume index determinations, one should determine for the centrifuge used, the volume of cells obtained on centrifuging a blood containing 5 million cells of normal size and consider this as 100 per cent.

In counting the red cells two preparations have been made from each of the two pipets filled and counted. This figure given for the red count thus represents four counts on each blood. Unless satisfactory checks were obtained, the counts were repeated. This is very important since we have found that the most frequent source of error in calculating the indices is in the red counts.

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<sup>9</sup> Van Slyke, D. D. *J. Biol. Chem.* 49 1, 1921

The counting chamber and pipets have been certified as correct by the Bureau of Standards. All other pipets used, the hematocrit tubes and the Van Slyke apparatus, have been recalibrated carefully by weighing with water.

The volume of packed cells taken as normal, or 100 per cent, namely, 46 c c of packed cells for 10 c c of blood containing 5 million cells per c mm, was calculated from the average of many normal bloods. In figuring the color index, 15.6 gm hemoglobin per hundred cubic centimeters of blood is taken as 100 per cent<sup>1</sup>. The saturation index is calculated by dividing the percentage of hemoglobin by the volume per cent of packed cells. The calculation of the three indices and the actual volume of hemoglobin content of the average red cell is best illustrated by an example.

*Example*—On centrifuging 10 c c of normal blood with a red cell count of 5 million per c mm, 46 c c of packed cells are obtained. On centrifuging a similar volume of blood from a patient with anemia, 31 c c are obtained. The red cell count is 2,500,000 per c mm. The volume index is

$$\frac{\frac{\text{Volume R B C obtained}}{\text{Normal volume}}}{\frac{\text{R B C per c mm}}{5,000,000}} = \frac{\frac{31}{46}}{\frac{2,500,000}{5,000,000}} = \frac{0.675}{0.500} = 1.35$$

The hemoglobin content of the blood of this patient is 9.36 gm per hundred cubic centimeters, or 60 per cent (Normal Standard). The color index, calculated in the usual way, is 1.20.

$$\text{The saturation index is } \frac{\text{Per cent of hemoglobin}}{\text{Volume per cent of cells}} = \frac{60}{67.5} = 0.89$$

$$\text{The individual cell volume is } \frac{31}{2,500,000 \times 1000 \times 10} = 12.4 \times 10^{-11} \text{ c c}$$

The hemoglobin content of the average cell is

$$\frac{9.6}{2,500,000 \times 1000 \times 100} = 3.74 \times 10^{-11} \text{ gm}$$

$$\text{The actual hemoglobin content of the red cell is } \frac{3.74 \times 10^{-11}}{12.4 \times 10^{-11}} = 30.2 \text{ per cent}$$

*Summary*—The blood of this patient, then, has a volume index of 1.35, a color index of 1.20, a saturation index of 0.89, average cell volume of  $12.4 \times 10^{-11}$  c c, an average cell hemoglobin content of  $3.74 \times 10^{-11}$ , and the hemoglobin in the cells is 30.2 per cent.

#### METHODS

The findings in normal blood are shown in Tables 1, 2, 3 and 4. It will be noted that the hemoglobin in grams per hundred cubic centimeter per 5 million cells is remarkably constant. The average in the series of normal men, ages 18 to 30, is 15.57 gm per hundred cubic centimeter, normal ages from 30 to 50, 15.65 gm, and normal women all ages, 15.65 gm. The average of all men and women is 15.6 gm.



TABLE 1—NORMAL MEN—AGES 18 TO 30

Age	R. B. C. in Millions per C Mm	Oxygen Capacity per 100 C c	Gm Hb per 100 C c	Hb in per Cent	Oxygen Capacity per 100 C c per 5 Million Cells	Hemoglobin in Gm per 100 C c per 5 Million Cells	Hematocrit Reading	Volume per Cent R B C	Volume Index	Color Index	Saturation Index	Volume Average Cell in C c $\times 10^{-11}$	Gm Hb in Average cell $\times 10^{-11}$	Actual Percentage Hb in cell
18	4.93	21.70	16.20	103	21.98	16.40	45.0	98	0.99	1.04	1.05	9.1	3.28	36.0
18	5.10	21.70	16.20	103	21.15	15.85	48.0	104	1.02	1.01	0.99	9.4	3.17	33.6
19	5.20	21.07	15.75	101	20.30	15.15	45.0	98	0.95	0.97	1.02	8.7	3.03	34.8
23	4.80	21.57	16.08	103	22.40	16.70	45.5	99	1.03	1.05	1.02	9.5	3.34	34.6
23	5.62	22.12	16.61	106	19.76	14.75	51.0	110	0.98	0.94	0.96	9.0	2.95	32.6
24	4.87	20.15	15.13	97	20.85	15.55	45.5	99	1.02	0.99	0.97	9.4	3.11	32.9
25	4.84	20.30	15.00	96	20.80	15.50	42.0	91	0.95	0.99	1.04	8.7	3.10	35.1
25	5.26	22.00	16.40	105	20.95	15.65	49.0	106	1.01	1.00	0.99	9.2	3.13	33.6
25	5.49	22.40	16.70	107	20.19	15.20	49.5	107	0.97	0.97	1.00	8.9	3.04	33.9
25	5.50	19.25	16.05	103	19.53	14.60	50.0	108	0.99	0.93	0.95	9.1	2.92	32.2
26	5.36	21.45	16.10	103	20.09	15.05	47.0	102	0.95	0.96	1.01	8.7	3.10	34.2
26	4.98	21.03	16.32	104	21.98	16.40	47.0	102	1.02	1.04	1.02	9.4	3.28	34.6
26	5.00	21.98	16.40	105	21.98	16.40	45.0	98	0.98	1.05	1.07	9.0	3.28	36.2
27	4.70	19.73	14.72	95	21.06	15.70	46.0	100	1.06	1.01	0.95	9.7	3.14	32.2
28	5.57	23.00	17.17	110	20.55	15.35	51.0	111	1.00	0.99	0.99	9.2	3.07	33.6
28	5.09	20.80	15.53	100	20.50	15.30	45.0	98	0.96	0.93	1.02	8.8	3.06	34.6
28	4.72	19.68	14.70	94	20.90	15.60	44.0	96	1.02	1.00	0.93	9.4	3.12	33.2
29	5.09	21.18	15.80	101	20.85	15.55	46.0	100	0.98	0.99	1.01	9.0	3.11	34.2
29	4.52	18.80	14.02	90	20.80	15.50	44.0	96	0.95	0.99	1.04	8.7	3.10	35.1
29	4.99	21.00	15.70	101	20.90	15.60	46.0	100	1.00	1.01	1.01	9.2	3.12	34.2
Average	5.08	21.20	15.83	101	20.85	15.57	46.5	101	1.00	1.00	1.00	9.2	3.11	33.9

TABLE 2—NORMAL MEN—AGES 30 TO 50

Age	R. B. C. in Millions per C Mm	Oxygen Capacity per 100 C c	Gm Hb per 100 C c	Hb in per Cent	Oxygen Capacity per 100 C c per 5 Million Cells	Hemoglobin in Gm per 100 C c per 5 Million Cells	Hematocrit Reading	Volume per Cent R B C	Volume Index	Color Index	Saturation Index	Volume Average Cell in C c $\times 10^{-11}$	Gm Hb in Average cell $\times 10^{-11}$	Actual Percentage Hb in cell
30	4.80	20.20	15.10	97	21.10	15.70	46.5	99	1.03	1.01	0.98	9.5	3.14	33.2
30	4.73	18.45	13.80	89	19.60	14.60	44.0	95	1.00	0.94	0.94	9.2	2.92	31.9
31	4.40	19.35	14.41	93	21.95	16.35	43.0	93	1.05	1.05	1.00	8.7	3.27	33.9
32	5.20	21.57	16.10	103	20.80	15.50	45.0	98	0.95	0.99	1.05	8.7	3.10	35.6
32	5.02	20.80	15.52	100	20.80	15.50	46.0	100	1.00	1.00	1.00	9.2	3.10	33.9
32	4.80	20.92	15.11	96	21.12	15.75	46.0	100	1.00	1.00	1.00	9.2	3.15	33.9
33	4.58	19.43	14.50	93	21.20	15.80	45.0	98	1.06	1.01	0.96	9.8	3.16	32.6
35	5.05	20.72	15.45	99	20.55	15.30	46.0	100	0.99	0.98	1.01	9.1	3.06	34.2
35	5.15	22.13	16.50	104	21.45	16.00	48.0	104	1.01	1.02	1.01	9.3	3.20	34.2
35	5.46	21.65	16.15	104	19.85	14.80	49.0	107	0.98	0.96	0.93	9.0	2.96	33.2
35	4.97	20.65	15.40	99	20.80	15.50	45.0	98	0.99	1.00	1.01	9.1	3.10	34.2
36	4.80	20.65	15.40	99	21.52	16.05	45.0	98	1.02	1.01	0.99	9.4	3.21	33.7
38	4.27	18.75	14.00	89	22.00	16.40	39.5	86	1.01	1.05	1.04	9.3	3.23	35.2
39	5.16	21.50	16.10	103	20.85	15.55	47.5	103	0.99	1.00	1.01	9.1	3.11	34.2
40	4.64	19.20	14.30	92	20.70	15.45	42.0	92	1.00	1.00	1.00	9.2	3.10	33.9
44	5.20	22.65	16.90	108	21.82	16.25	49.0	107	1.02	1.03	1.01	9.4	3.25	34.2
44	4.56	19.00	14.20	91	20.85	15.55	42.0	92	1.01	1.00	0.99	9.3	3.11	33.6
49	4.82	18.75	14.00	89	21.80	16.20	40.0	87	1.00	1.03	1.03	9.2	3.24	34.9
50	4.89	20.90	15.60	100	21.30	15.90	44.5	97	0.99	1.02	1.02	9.1	3.18	34.6
50	5.28	21.55	16.10	103	20.25	15.25	48.0	104	0.99	0.98	0.99	9.1	3.05	33.6
Average	4.865	20.25	15.23	98	21.00	15.65	45.0	98	1.00	1.00	1.00	9.2	3.13	33.9

which figure is taken as 100 per cent in calculating the hemoglobin in per cent and in determining the color index and the saturation index. The color and volume index vary only within the limits of error of the determination, namely 0.95 and 1.05. The average is exactly 1.00. The saturation index varies within the same limits with an average of 1.00. The volume and hemoglobin content of the normal cell varies

TABLE 3—NORMAL WOMEN

Age	R B C in Millions per C Mm	Oxygen Capacity per 100 C c	Gm Hb per 100 C c	Hb in per Cent	Oxygen Capacity per 100 C c per 5 Million Cells	Hemoglobin in Gm per 100 C c per 5 Million Cells	Hematoerit Reading	Volume per Cent R B C	Volume Index	Color Index	Saturation Index	Volume Average Cell in C c $\times 10^{-11}$	Gm Hb in Average cell $\times 10^{-11}$	Actual Percentage Hb in cell
20	4.15	17.70	13.20	84	21.30	15.90	38.0	83	1.00	1.01	1.01	9.2	3.18	34.2
21	3.89	16.23	12.12	78	21.90	15.60	36.0	79	1.01	1.01	1.00	9.3	3.13	33.9
22	4.20	17.49	13.10	84	20.90	15.60	38.0	83	0.99	1.00	0.99	9.1	3.13	33.6
23	4.40	18.07	13.50	87	20.55	15.35	40.5	88	1.00	1.00	1.00	9.2	3.07	33.9
25	4.45	18.60	13.88	88	20.90	15.60	41.0	90	1.01	0.99	0.98	9.3	3.12	33.2
26	4.38	19.90	14.80	95	22.60	16.90	43.0	93	1.05	1.03	1.03	9.7	3.38	34.9
27	4.72	19.56	14.60	94	20.70	15.45	43.0	94	1.00	1.00	1.00	9.2	3.09	33.9
27	3.97	15.90	11.90	76	20.10	15.00	37.0	80	1.02	0.97	0.95	9.4	3.00	32.2
30	4.56	18.75	14.00	90	20.55	15.35	41.0	90	0.99	0.99	1.00	9.1	3.07	33.9
33	3.95	16.20	12.10	78	20.55	15.30	37.0	80	1.01	0.99	0.98	9.3	3.06	33.2
40	4.31	17.98	13.40	86	20.90	15.60	40.0	87	1.02	1.00	0.98	9.4	3.12	33.2
40	4.26	18.05	13.50	86	21.15	15.85	39.0	85	1.00	1.01	1.01	9.2	3.17	34.2
Average	4.26	17.33	13.34	85	21.00	15.65	39.0	85	1.00	1.00	1.00	9.2	3.13	33.9

TABLE 4—MEN AND WOMEN OF ALL AGES

R B C in Millions per C Mm	Oxygen Capacity per 100 C c	Gm Hb per 100 C c	Hb in per Cent	Oxygen Capacity per 100 C c per 5 Million Cells	Hemoglobin in Gm per 100 C c per 5 Million Cells	Hematoerit Reading	Volume per Cent R B C	Volume Index	Color Index	Saturation Index	Volume Average Cell in C c $\times 10^{-11}$	Gm Hb in Average cell $\times 10^{-11}$	Actual Percentage Hb in cell	
5.08	21.20	15.83	101	20.85	15.57	46.5	101	1.00	1.00	1.00	9.2	3.11	33.9	Average men 18-30
4.865	20.25	15.23	98	21.00	15.65	45.0	98	1.00	1.00	1.00	9.2	3.13	33.9	Average men 30-50
4.26	17.33	13.34	85	21.00	15.65	39.0	85	1.00	1.00	1.00	9.2	3.13	33.9	Average women all ages
4.74	19.86	14.80	95	20.90	15.62	43.5	95	1.00	1.00	1.00	9.2	3.12	33.9	Average all men and women

little. The average volume of the cells in men and women is  $9.2 \times 10^{-11}$  c c. Starling<sup>10</sup> states that the normal cell volume is  $7.22 \times 10^{-11}$  c c. Luciani<sup>11</sup> gives it as  $6.67 \times 10^{-11}$  c c. The former results are based on determinations with models of high magnification. Our figure is higher than the figures quoted. It is possible that some plasma may

<sup>10</sup> Starling, E. H. Principles of Human Physiology, Philadelphia, Lea & Febiger, 1915, p. 818.

<sup>11</sup> Luciani, L. Human Physiology, New York, Macmillan & Co. 1915, p. 105.

remain in the packed cells giving readings which are somewhat too high. The centrifuge used was a very powerful one, however, and maximum packing was attained so it is difficult to see how any fluid could remain in the interstices between the cells. The average hemoglobin content of the cells varies little in men and women, the average being  $3.12 \times 10^{-11}$  gm. The actual percentage of hemoglobin in the red cells is 33.9. There are no variations from this beyond the limits of error.

*Pernicious Anemia*—The findings in pernicious anemia present a marked contrast to those of normal blood (Table 5). The bloods

TABLE 5—PERNICIOUS ANEMIA

R. B. C. in Millions per C. Mm.	Oxygen Capacity per 100 C. c.	Gm. Hb. per 100 C. c.	Hb. in per Cent	Oxygen Capacity per 100 C. c. per 5 Million Cells	Hemoglobin in Gm. per 100 C. c. per 5 Million Cells	Hematocrit Reading	Volume per Cent R. B. C.	Volume Index	Color Index	Saturation Index	Volume Average Cell in C. c. $\times 10^{-11}$	Gm. Hb. in Average cell $\times 10^{-11}$	Actual Percentage Hb. in cell	Remarks
0.74	3.83	2.76	18	25.95	18.35	10.0	21	1.41	1.21	0.86	13.0	3.87	29.2	Large spleen
1.24	3.53	2.63	17	14.15	10.55	15.0	33	1.31	0.69	0.52	12.1	2.11	17.6	
1.38	6.24	4.65	30	22.60	16.85	15.0	33	1.21	1.09	0.90	11.1	3.37	30.5	
1.42	8.90	6.65	43	31.40	23.40	19.5	42	1.47	1.51	1.02	13.5	4.63	34.6	
1.58	9.15	6.80	44	28.85	21.50	21.0	46	1.45	1.39	0.96	13.4	4.30	32.6	
1.64	9.55	7.13	46	29.15	21.75	21.0	46	1.39	1.39	1.00	12.8	4.35	33.9	
1.61	7.79	5.60	37	23.30	17.40	18.0	39	1.22	1.16	0.93	11.2	3.48	31.5	Primary aplastic type
1.63	8.30	6.20	40	24.75	18.45	18.5	40	1.20	1.20	1.00	11.1	3.69	33.9	
1.73	7.90	5.89	38	22.80	17.00	22.0	48	1.38	1.10	0.79	12.7	3.40	26.8	Ataxia, fixed pupils
1.75	9.87	7.35	47	28.20	21.00	21.0	46	1.31	1.31	1.00	12.1	4.20	33.9	
1.81	8.27	6.15	39	22.80	17.00	22.0	48	1.33	1.08	0.82	12.3	3.40	27.8	
1.88	12.33	9.22	59	32.85	24.50	29.0	63	1.63	1.57	0.93	15.5	4.90	31.5	Very marked cord changes
1.99	10.09	8.20	52	27.60	20.60	26.0	56	1.40	1.30	0.93	12.9	4.12	31.5	
2.10	11.50	8.59	55	27.40	20.45	25.0	54	1.35	1.30	0.96	12.4	4.09	32.6	
2.27	7.98	5.95	38	17.50	13.05	37.0	81	1.77	0.84	0.47	16.3	2.61	16.0	
2.33	12.17	9.08	58	26.15	19.50	28.5	62	1.33	1.24	0.94	12.2	3.90	31.9	
2.60	10.18	7.60	49	19.60	14.60	28.0	61	1.17	0.94	0.80	10.8	2.92	27.1	Remission for six years
2.79	13.60	10.20	65	24.50	18.30	32.0	69	1.23	1.16	0.94	11.3	3.66	31.9	
2.93	17.29	12.90	82	29.50	22.00	36.5	79	1.35	1.39	1.03	12.4	4.40	34.9	
3.33	16.40	12.20	80	24.60	18.35	37.0	81	1.20	1.20	1.00	11.1	3.67	33.9	Remission for ten years
1.94	9.75	7.28	47	25.15	18.75	24.5	53	1.39	1.21	0.89	12.8	3.75	30.2	Average

examined cover a wide range of red cell count and hemoglobin content. The counts vary from 0.74 million to 3.33 millions per c. m., and the hemoglobin varies from 3.83 to 12.20 gm. per hundred cubic centimeter. The volume per cent of red cells as determined by the hematocrit method is uniformly high. The volume index ranges from 1.17 to 1.77. The average is 1.39. The color index is below 1.00 in only three instances and is never higher than the volume index. The saturation index is as high as 1.00 in only six of the twenty cases and is never over 1.00 beyond the limits of error.

The cause of the high color index in pernicious anemia is still not clear in the minds of many. I find on inquiry that most physicians

believe that there is a supersaturation of the cells with hemoglobin. Although Capps pointed out that the color index is never higher than the volume index, and the high color index is thus due to the increase in cell volume, this fact is not made clear in even the most recent text books. The term hyperchromemia is frequently used in the sense of a

TABLE 6—HEMOLYTIC SECONDARY ANEMIA

R B C in Millions per O Mm	Oxygen Capacity per 100 C c	Gm Hb per 100 C c	Hb in per Cent	Oxygen Capacity per 100 C c per 5 Million Cells	Hemoglobin in Gm per 100 C c per 5 Million Cells	Hematocrit Reading	Volume per Cent R B C	Volume Index	Color Index	Saturation Index	Volume Average Cell in C c $\times 10^{-11}$	Gm Hb in Average cell $\times 10^{-11}$	Actual Percentage Hb in cell	Diagnosis
1.60	5.63	4.20	27	17.55	13.10	17.5	33	1.04	0.91	0.71	9.6	2.62	24.1	Chronic nephritis
1.96	7.25	5.40	35 <sup>1</sup>	18.50	13.80	18.0	39	1.00	0.90	0.90	9.2	2.76	30.5	Carcinoma of stomach
2.67	9.25	6.90	44	17.30	12.90	24.0	52	0.98	0.82	0.85	9.0	2.58	28.8	Chronic bronchitis
2.85	8.22	6.13	39	13.95	10.40	25.0	54	0.95	0.68	0.72	8.7	2.08	24.4	Carcinoma of cervix
2.94	5.62	4.20	27	9.53	7.15	22.0	47	0.79	0.46	0.57	7.3	1.43	19.7	Undetermined
3.10	8.93	6.70	43	14.63	10.90	23.0	50	0.70	0.80	0.88	6.4	2.18	29.0	Diffuse carcinoma
3.21	10.90	8.14	52	16.81	12.55	30.0	65	1.01	0.81	0.80	9.3	2.51	27.2	matosis
3.31	10.23	7.87	50	15.78	11.85	28.0	61	0.92	0.76	0.83	8.5	2.37	28.2	Lead poisoning
3.35	12.32	9.15	59	18.15	13.55	31.0	68	1.03	0.88	0.87	9.5	2.71	29.5	Carcinoma of stomach
3.36	9.04	6.75	43	13.48	10.05	24.0	52	0.78	0.64	0.83	7.2	2.01	28.2	Acute endocarditis
3.36	13.65	10.20	65	20.30	15.15	31.0	63	1.01	0.97	0.96	9.3	3.03	32.6	Chronic nephritis
3.54	12.80	11.03	71	20.85	15.55	33.5	73	1.02	1.00	0.98	9.4	3.11	33.2	Pelvic inflammatory disease
3.63	16.50	12.30	79	22.63	16.95	32.5	71	0.96	0.92	1.04	7.2	3.39	35.3	Chronic nephritis
3.93	15.80	11.77	75	20.10	15.00	38.0	83	1.05	0.95	0.90	9.7	3.00	30.5	Malnutrition
4.03	16.30	12.15	78	20.25	15.10	37.0	81	1.00	0.96	0.96	9.2	3.02	32.6	Undetermined
4.10	9.05	6.75	43	11.03	8.25	29.0	63	0.77	0.52	0.63	7.1	1.65	23.1	Obstruction common bile duct
4.11	17.15	12.82	82	20.85	15.55	39.0	85	1.04	1.00	0.96	9.6	3.11	32.6	Wassermann 4+, luetic?
4.15	12.82	9.55	61	15.40	11.50	32.0	69	0.83	0.74	0.80	7.6	2.30	30.2	Carcinoma of colon
4.60	17.60	13.15	84	19.30	14.40	43.0	94	1.02	0.91	0.92	9.4	2.88	31.2	Pelvic inflammatory disease
4.61	16.85	12.58	80	18.15	15.55	44.0	95	1.03	0.87	0.85	9.5	2.71	28.8	Chronic focal infection
4.72	16.83	12.56	80	17.82	13.30	44.0	95	1.00	0.85	0.85	9.2	2.66	28.8	Mild chlorosis
4.99	11.75	8.77	56	11.70	8.80	34.0	75	0.75	0.56	0.71	6.9	1.76	24.1	Chronic bronchitis
5.00	16.75	12.48	80	16.75	12.50	42.0	92	0.92	0.80	0.87	8.5	2.50	29.5	General gland enlargement
5.04	14.41	14.47	93	19.22	14.35	45.0	98	0.93	0.93	0.95	9.0	2.87	32.2	Catarthal jaundice
5.08	17.67	13.20	85	17.41	13.00	44.0	96	0.95	0.84	0.89	8.7	2.60	30.4	Conv acute tonsillitis
5.10	11.10	8.28	53	11.10	8.30	32.0	70	0.63	0.52	0.78	6.3	1.66	26.5	Acetanilid poisoning
3.78	12.75	9.52	61	17.00	12.70	32.0	70	0.93	0.81	0.87	8.6	2.52	29.5	Undetermined
														Average

supersaturation. Likewise, Larrabee did not find the volume index constantly higher than the color index. Our series in which exact methods are used verifies the statement of Capps. The saturation index is of value in emphasizing this point, since it is never more than 1.00 and is seldom as high as 1.00. The average percentage of hemoglobin in the cells is 30.2 as compared with a normal of 33.9.

The average cell volume is variable but always greater than the normal. The average of the twenty cases is  $128 \times 10^{-11}$ , or 39 per cent greater than the average normal. The average hemoglobin content of the cell is  $3.75 \times 10^{-11}$  gm, or 21 per cent greater than normal.

Several cases in this series are of special interest. Case 8 was a typical case of aplastic anemia of four months' duration. The volume index was 1.22 and the color index was 1.16. The last two cases are unusually interesting. One patient has had a remission of six years, the other of ten years. In each instance there is at present a very high color and volume index. Free hydrochloric acid is still absent on gastric analysis. The patients are, however, free of symptoms. These

TABLE 7—HEMORRHAGIC SECONDARY ANEMIA

R. B. C. in Millions per C. Mm.	Oxygen Capacity per 100 C. c.	Gm. Hb. per 100 C. c.	Hb. in per Cent	Oxygen Capacity per 100 C. c. per 5 Million Cells	Hemoglobin in Gm. per 100 C. c. per 5 Million Cells	Hematocrit Reading	Volume per Cent R. B. C.	Volume Index	Color Index	Saturation Index	Volume Average Cell in C. c. $\times 10^{-11}$	Gm. Hb. in Average cell $\times 10^{-11}$	Actual Percentage Hb. in cell	Diagnosis
1.37	3.18	2.37	15	10.50	7.85	9.5	20	0.73	0.59	0.81	6.7	1.73	20.0	Intestinal hemorrhage
3.00	7.74	5.77	37	12.85	9.60	22.0	47	0.78	0.62	0.79	7.2	1.92	21.0	Hemorrhoids, examined 5/24/21
3.38	8.74	6.52	42	12.90	9.65	25.0	54	0.80	0.62	0.78	7.4	1.93	21.0	Same patient, examined 7/5/21
4.95	13.27	9.90	53	13.47	10.05	36.0	78	0.77	0.60	0.75	7.4	1.00	20.4	Hemorrhoids, examined 3/7/22
3.43	7.02	5.23	34	8.92	6.65	21.0	46	0.67	0.50	0.75	6.2	1.53	17.0	Same patient, examined 4/3/22
3.96	9.40	7.02	45	11.85	8.85	28.0	60	0.76	0.57	0.75	7.0	1.77	19.7	Hemorrhoids
3.93	11.97	8.91	57	15.80	11.40	31.0	67	0.75	0.73	0.85	6.9	2.28	24.8	Gastric ulcer
4.50	12.83	9.62	62	14.35	10.70	32.0	70	0.77	0.70	0.90	7.1	2.14	23.8	Carcinoma of cervix
3.57	9.30	6.92	44	13.00	9.70	25.0	55	0.77	0.62	0.80	7.1	1.94	21.0	Average

findings lend weight to the belief of many clinicians that "once pernicious anemia, always pernicious anemia."

*Hemolytic Secondary Anemia*—The secondary anemias have been classified roughly into two types. The anemias due to increased blood destruction within the blood vessels are considered as hemolytic, those due to the loss of blood through hemorrhage as hemorrhagic. This is obviously an unsatisfactory classification but serves the present purpose. Twenty-six observations on hemolytic anemia are recorded (Table 6). These show for the most part a volume index of 1.00 or very little less regardless of the extent of the anemia. The cases presenting a low volume index have probably existed for a long time, the low index being due to long continued drain on the bone marrow. The average volume index of this group is 0.93, the color index, 0.81, and the saturation index, 0.87.

The volume of the average cell in the average of the series is  $86 \times 10^{-11}$  c c and the average hemoglobin content is  $25 \times 10^{-11}$  gm. It is of interest to note that the saturation index and the actual percentage of hemoglobin in the red cells is very nearly equal that of pernicious anemia.

Capps reported a volume index greater than 1.00 in certain cases of jaundice. I have examined the blood of two persons with this condition. In one case the jaundice was due to a catarrhal cholangitis, in the other to an obstruction of the common bile duct by a carcinoma of the head of the pancreas. The jaundice was most intense in both instances. The volume index is 1.00 in one, and 0.92 in the other. Several cases of carcinoma are recorded, including two involving the stomach. The volume index is 1.00 or less.

*Hemorrhagic Secondary Anemia*—Only eight cases were studied in this group. The results are tabulated in Table 7. These patients had all suffered from chronic hemorrhage. The volume index is low in every instance, the average being 0.77. The color index is still lower, namely 0.62. The saturation index is higher than either the color or volume index, the average being 0.80. In the final average the cell volume is  $71 \times 10^{-11}$  c c. The hemoglobin content of the average cell is  $1.94 \times 10^{-11}$  gm. The actual percentage of hemoglobin in the red cells is 27.1. No opportunity has presented itself to study cases of acute hemorrhage. It is apparent that in anemia due to very acute hemorrhage there could be no change in volume index. In the cases reported the very low volume of the average red cell is probably the best index of the drain on the bone marrow.

#### DISCUSSION

The results obtained in this study emphasize in a striking way the great constancy of the volume and hemoglobin content of the normal cell. No variations greater than the limits of error incident to the determination have been encountered. The fact that the hemoglobin in normal blood never exceeds a concentration of 33.9 per cent can be accepted as the strongest evidence that this figure represents the saturation of the red cells by hemoglobin.

In pernicious anemia the one constant and characteristic feature of the blood is the increased volume of the average red cell. This increased volume has not so far been found in any other condition and it would seem that a volume index beyond the limits of error of the determination is almost diagnostic of pernicious anemia. A color index greater than 1.00 means only that the cells are larger than normal. The volume index of more than 1.00 is always present if the color index

is greater than 100 and also in many instances in which the color index is less than 100. It is obvious that a knowledge of the volume index is of greater value than the color index in differential diagnosis of the different types of anemia.

The facts presented on the exact volume and hemoglobin content of the average cell in pernicious anemia expressed in absolute instead of relative terms prove beyond question that supersaturation of red

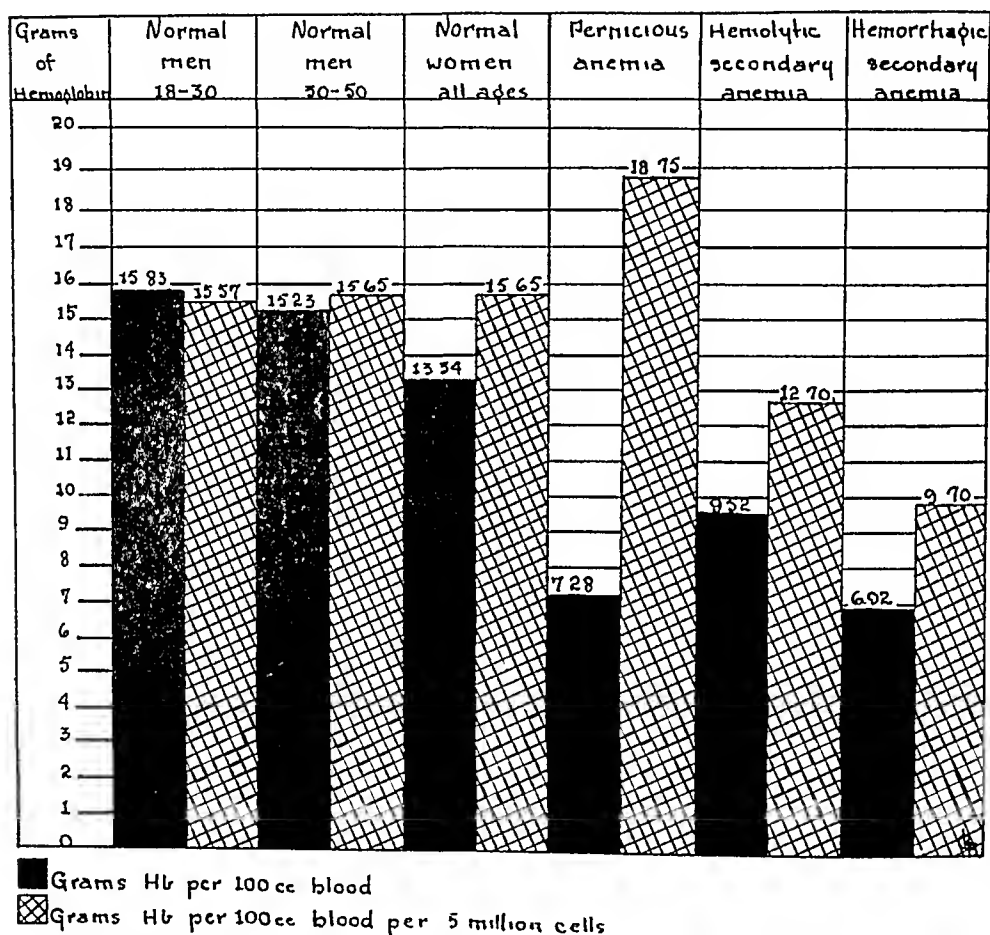


Fig 1—Hemoglobin percentage of blood of normal persons and in cases of anemia

cells never occurs. This is most graphically shown in the single case by the calculation of the saturation index which expresses the amount of hemoglobin in the cell relative to normal, and in every case is 100, or less.

A variation in volume of the red cells is very much more easily determined than a variation in the diameter of the cell. A relatively small increase in diameter causes a very large increase in cell volume.

This is illustrated in Figure 2 To give an increase of 39 per cent in the volume of the cells it is only necessary to increase the diameter of every cell from the normal 760 microns, to 848 microns If the increase is uniform, involving all the cells, as is not uncommonly the case, it is most difficult to detect the increase in size of the red cells by simply looking at them in a fresh preparation or on a stained film

Price-Jones<sup>12</sup> thinks that there is a diurnal variation in size of the cells His claim is based on results obtained by measuring the diameter of the cells The variation in diameters which he describes would make a very large difference in volume I have made determinations of the

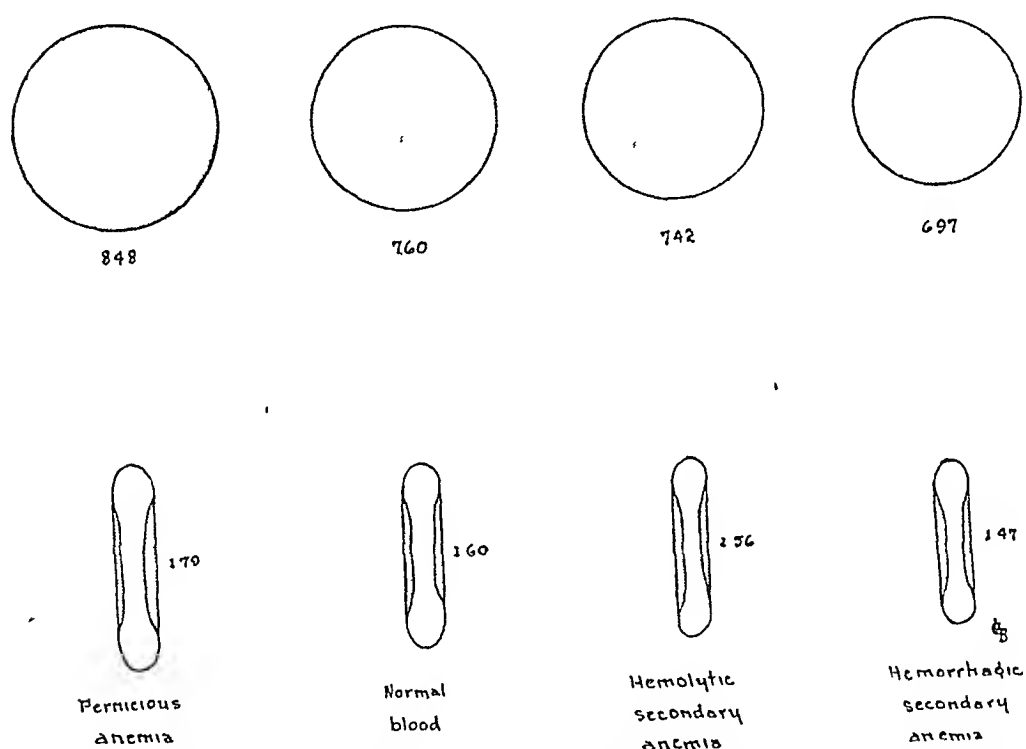


Fig 2—Diagram to illustrate the relative measurements of the red blood cell in the various anemias as compared with the normal

cell volume by the method described at all times of the day and find no evidence of a diurnal variation

As contrasted with primary anemia, the secondary anemias show an average cell volume never greater than normal and seldom as large. The color index is correspondingly smaller. The saturation index, however, is nearly as great as that in pernicious anemia. The per cent of saturation of the hemoglobin in the protoplasm probably plays a large part in its ability to transport oxygen. This preservation of concentration is perhaps a protective phenomenon. The smaller size



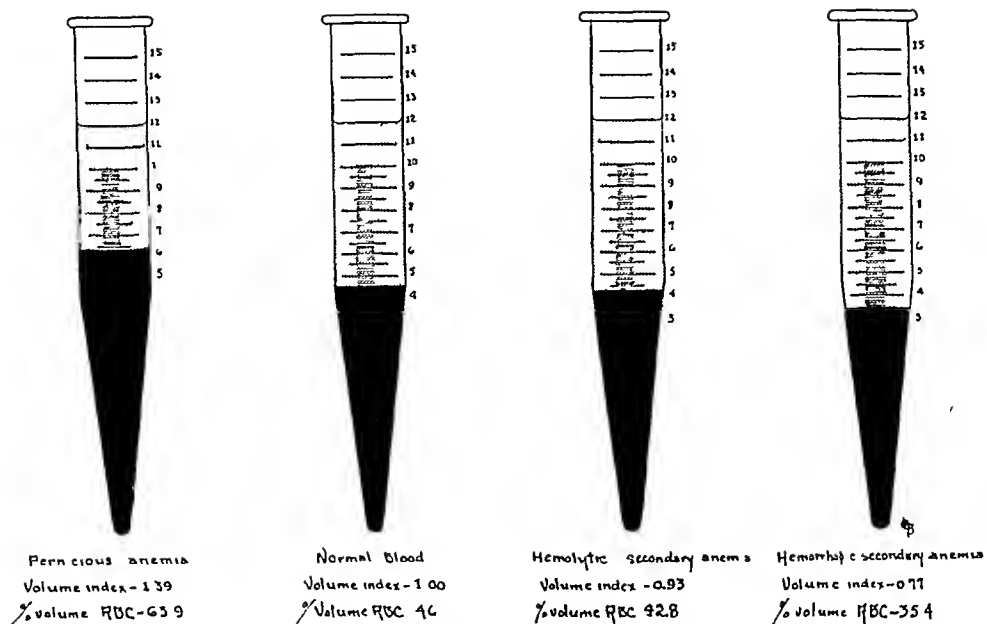


Fig 3—Diagram to illustrate the volume of packed red corpuscles obtained on centrifuging 10 cc of blood containing 5 million red cells per cubic millimeter

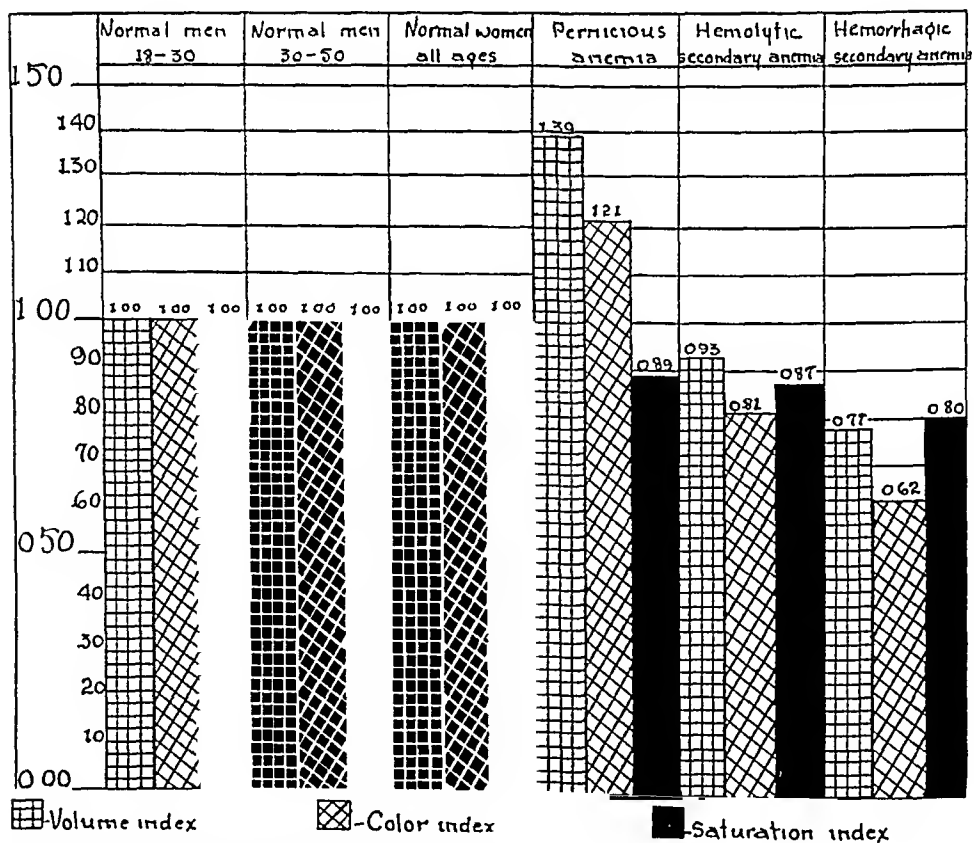


Fig 4—Diagram to show the volume, color, and saturation index in normal blood and in the anemias

of the cell in hemorrhagic anemia is probably the direct result and an expression of the long continued drain on the bone marrow

The best comparison of the difference in cell mass in different types of blood is best shown by the actual volume of cells obtained on centrifuging a certain amount of blood. If we suppose that the blood from different types of anemias were concentrated so that there would be 5,000,000 cells per cubic centimeter as in the normal, and 10 c c of each were centrifuged, the cell volume would be as illustrated in Figure 3. The figures given represent the average of the cells in different groups studied. It will be noted that the cell volume in pernicious anemia is almost twice that of hemorrhagic secondary anemia.

The relation of the three indices in all the groups is illustrated in Figure 4. The indices are equal only in normal blood.

TABLE 8—COMPARISON OF AVERAGE FINDINGS IN NORMAL BLOOD AND IN THE ANEMIAS

R B C in Millions per C Mm	Oxygen Capacity per 100 C c	Gm Hb per 100 C c	Hb in per Cent	Oxygen Capacity per 100 C c per 5 Million Cells	Hemoglobin in Gm per 100 C c per 5 Million Cells	Hematocrit Reading	Volume per Cent R B C	Volume Index	Color Index	Saturation Index	Volume Average Cell in C c $\times 10^{-11}$	Gm Hb in Average cell $\times 10^{-11}$	Actual Percentage Hb in cell	
5.08	21.20	15.83	101	20.85	15.57	46.5	101	1.00	1.00	1.00	92	3.11	33.9	Average men 18-30
4.865	20.25	15.23	98	21.00	15.65	45.0	98	1.00	1.00	1.00	92	3.13	33.9	Average men 30-50
4.26	17.33	13.34	85	21.00	15.65	39.0	85	1.00	1.00	1.00	92	3.13	33.9	Average women all ages
4.74	19.86	14.80	95	20.95	15.62	43.5	95	1.00	1.00	1.00	92	3.12	33.9	Average all men and women
1.94	9.75	7.28	47	25.15	18.75	24.5	53	1.39	1.21	0.89	12.8	3.75	30.2	Average pernicious anemia
3.78	12.75	9.52	61	17.00	12.70	32.0	70	0.93	0.81	0.87	8.6	2.52	29.5	Average hemolytic secondary anemia
3.57	9.30	6.92	44	13.00	9.70	25.0	55	0.77	0.62	0.80	7.1	1.94	27.1	Average hemorrhagic secondary anemia

#### SUMMARY AND CONCLUSIONS

A study is presented of the red cell count, hemoglobin in grams per hundred cubic centimeters, volume index, saturation index, the exact volume and the exact hemoglobin content, and the hemoglobin percentage in the red cells of the blood of fifty-two normal men and women, twenty cases of pernicious anemia, twenty-six cases of hemolytic secondary anemia, and eight cases of hemorrhagic anemia.

A new index which expresses the hemoglobin saturation of the red cells as compared with the normal is described. In normal blood the red cells are completely saturated with hemoglobin, hence the index is always 1.00.

A study of the volume of the cells is of the greatest value in the differential diagnosis of the anemias. The volume is best expressed as the volume index of Capps.

When determined by exact and absolute methods the volume index, the color index, and the saturation index of normal blood are always 1 00 within the limits of error

In normal blood the volume of the average red cell is  $92 \times 10^{-11}$  gm, and the percentage of hemoglobin in the red cells is 33 9

In pernicious anemia the practically constant and the most characteristic blood findings is the large volume of the average red cell, as shown by a volume index above 1 00

A volume index greater than 1 00 has not been found in any condition other than pernicious anemia

In pernicious anemia the increase in volume of the cell is greater than the increase in hemoglobin. The volume index is consequently always greater than the color index, and the saturation index is never above 1 00 and is seldom as high as 1 00. Supersaturation of the cells by hemoglobin never occurs

In the twenty cases of pernicious anemia studied, the average volume index is 1 39, the color index 1 21, and the saturation index 0 89. The volume of the cell is  $128 \times 10^{-11}$ , the grams of the hemoglobin  $3.75 \times 10^{-11}$  and the percentage of hemoglobin in the cell is 30 2

In hemolytic secondary anemia the volume of the cell is very little decreased unless there is prolonged drain on the bone marrow, hence the volume index is nearly 1 00. Likewise the color and saturation indices vary only a little from the normal

In the twenty-six cases of hemolytic secondary anemia studied, the average volume index is 0 93, the color index 0 81, and the saturation index 0 87. The volume of the cell is  $86 \times 10^{-11}$  c c, the hemoglobin content is  $2.52 \times 10^{-11}$  gm, and the percentage of hemoglobin is 29 5

The red cells in chronic hemorrhagic secondary anemia have a smaller volume than normal. The extent of the decrease is probably the best index of the drain on the bone marrow and is of definite prognostic value

Only eight cases of hemorrhagic secondary anemia have been studied. The average volume index is 0 77, the color index 0 62, and the saturation index 0 80. The volume of the average cell is  $71 \times 10^{-11}$ , the hemoglobin content is  $1.94 \times 10^{-11}$  gm, and the percentage of hemoglobin in the cells is 27 1

The percentage of hemoglobin in the cells is very nearly as high per unit volume of cells in secondary anemia as in primary anemia. The difference is in the size of the cells in the two conditions

## BOOK REVIEWS

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LEHRBUCH DER PATHOLOGISCHEN PHYSIOLOGIE FÜR STUDENTEN UND AERZTE Herausgegeben von Prof Dr H Ludke, und Prof Dr C Schlayer Paper Price, 540 marks Pp 819, with 133 illustrations Leipzig Johann Ambrosius Barth, 1922

Under the title mentioned are collected chapters by representative German authors on a variety of physiologic subjects, with discussions of the related functional pathology Franz Fischler has written the section on metabolism He mentions methods for studying metabolism, the nitrogen balance, caloric values of food substances, and discusses the importance of various organs, such as the liver, pancreas, and other organs which regulate the normal metabolism While this section contains much useful information, there is little reference to investigations completed during the last ten years No mention is made of basal metabolism, or of the work by Du Bois and his associates, neither is the buffer mechanism of the body fluids discussed in any way

A brief discussion on constitutional pathologic physiology is written by R v d Velden

Hans Eppinger's chapters on the glands of internal secretion are well written, and his literature references indicate a wide and thoroughly modern conception of facts known in this hazy field of medical biology

H Ludke contributes the section on infection and immunity Portals of bacterial invasion, defenses of the body, virulence of bacteria, bacterial toxins, natural and acquired immunity and other related features of this topic are discussed Anything particularly new is not contained, for practically all of the information mentioned has appeared in texts five or more years ago

Erich Leschke has written the chapters on fever—a review of features generally known and presented well

The physiology of the nervous system is written by E Forster, that of the circulation by C J Rothberger, of the respiration by Joseph Forschbach, of the blood and blood forming organs (including pathologic physiology) by Hans Hirschfeld, of digestion by J Strasburger, of nutrition by L Lichtwitz, and of the kidney by C R Schlayer Each of these sections contains an extensive discussion on a par with similar chapters in standard American medical physiologies

The book contains, in brief, considerable information regarding the subjects discussed It cannot be recommended to physicians generally as a model text, for practically all the information contained is in standard physiologies and in texts on bacteriology or immunity

THE CHEMISTRY OF TUBERCULOSIS A Compilation and Critical Review of Existing Knowledge on the Chemistry of the Tubercle Bacillus and Its Products, The Chemical Changes and Processes in the Host, The Chemical Aspects of the Treatment of Tuberculosis By H Gideon Wells, M D, Ph D, Professor of Pathology in the University of Chicago, Lydia M DeWitt, M D, A M, Associate Professor of Pathology in the University of Chicago, and Esmond R Long, Ph D, Assistant Professor of Pathology in the University of Chicago Cloth Price, \$5 Pp 447 Baltimore Williams & Wilkins Company, 1923

The increasing activity in research medicine in America becomes apparent in the number of monographs published during recent years This most recent addition to the list summarizes the careful reading as well as the more recent

work of the members of the Sprague Institute interested more particularly in tuberculosis. The publishers state that it is a complete reference handbook on the chemical aspects of tuberculosis and related problems. It is that. The material is quite recent, the presentation is well balanced, and seemingly nothing of importance has escaped consideration. It is invaluable to the worker in tuberculosis.

It is certainly refreshing and perhaps significant to note that the term "antibody" finds no place in the index. We are apparently advancing in our knowledge of tuberculosis when speculation gives place to accurate observation of biochemical and biophysical processes.

**MULTIPLE SCLEROSIS (DISSEMINATED SCLEROSIS)** An Investigation by The Association for Research in Nervous and Mental Diseases. Report of the Papers and Discussions at the Meeting of the Association, New York City, December 27th and 28th, 1921. Editorial Board: Charles L. Dana, M.D., Smith Ely Jelliffe, M.D., Henry Alsop Riley, M.D., Frederick Tilney, M.D., Walter Timme, M.D. Cloth. Price, \$3.75. Pp 241, with illustrations. New York: Paul B. Hoeber, 1922.

This book consists of papers on all phases of the subject by twenty-six prominent American investigators of nervous diseases, together with questions and comments by members of the "Commission" of the Association, and conclusions by the commission as a whole. The most interesting chapter is that by G. B. Hassin on the pathology. He considers the lesions as purely degenerative, not inflammatory, a view not shared by some of those present, as seen from the record of the animated discussion. The book can be recommended as setting forth in a novel and fascinating manner all that is known about this peculiar disease, including the results of the most recent researches in many countries.

## THE CLINICAL SIGNIFICANCE OF ABNORMALITIES IN URINE VOLUMES<sup>1</sup>

T ADDIS, M D

SAN FRANCISCO

The words oliguria, polyuria and nycturia are used in this paper to indicate different types of abnormality in urine volume, although in most dictionaries they have a double meaning and may designate changes either in the frequency of urination or in the amount of urine.

At present these words can be used only in a general descriptive sense, and are only applicable with any certainty in those instances in which the deviation from the volumes ordinarily observed is extreme. This is so not on account of any lack of measurements of the volume of urine in normal persons but because these measurements have been made under such varying conditions that the range of normal variation is wide and its limits uncertain. A definition of oliguria, polyuria and nycturia which would give the terms a quantitative significance requires a statistical determination of the distribution of the urine volumes of normal subjects under carefully selected and controlled conditions.

The conditions most likely to lead to the sharpest differentiation between the volumes from normal persons and those obtained from patients with Bright's disease may be expected to be of such a nature that they impose a strain either on the water excreting capacity of the kidney or on its concentrating capacity. For when a large amount of water is given to a patient whose effective renal tissue has been extremely reduced by disease the volume of urine excreted is much less than normal, while it is greater than normal when no fluids have been taken. Under one set of conditions the volume is too large and under the other set of conditions too small. In either case the volume of urine eliminated by a badly damaged kidney differs widely from the normal, and both conditions are, therefore, suitable for a statistical definition of oliguria, polyuria and nycturia.

### I OLIGURIA, POLYURIA

#### A CONDITIONS

*Constant Low Water Intake, Urea Administration, Twenty-Four Hour Collections*—In 1916, Addis and Watanabe<sup>1</sup> gave the volumes of

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\* From the Department of Medicine of Stanford University Medical School

<sup>1</sup> Addis and Watanabe J Biol Chem 27 267 1916

urine observed in twenty normal adults who were on a constant diet with a total water content of 1,710 c c. This diet was maintained for six days, and at the commencement of each of the last three twenty-four hour periods 20 gm of urea, dissolved in 360 c c of water, were taken. Since then, additional observations have been made on normal adults so that we now have measurements on twenty-eight persons. In order to decrease the variability, the twenty-four hour volumes of the fourth, fifth and sixth days have been averaged. The mean of these averages is 1,345 c c, the standard deviation is  $\pm 178$  c c and the variability is 13.2 per cent. Table 1 gives the odds against any

TABLE 1—DEFINITION OF OLIGURIA AND POLYURIA

Conditions Constant low water intake, urea administration twenty-four hour collections

Definition	Volume C c	Odds
Oliguria	775 or less	One normal in 1,450
	793 or less	One normal in 1,030
	811 or less	One normal in 741
	829 or less	One normal in 527
Doubtful	847 or less	One normal in 385
	864 or less	One normal in 286
	882 or less	One normal in 213
	900 or less	One normal in 162
	918 or less	One normal in 122
	936 or less	One normal in 93
	953 or less	One normal in 72
Normal	971 or less	One normal in 56
	1,345 or less	One normal in 2
Doubtful	1,719 or more	One normal in 56
	1,737 or more	One normal in 72
	1,754 or more	One normal in 93
	1,772 or more	One normal in 122
	1,790 or more	One normal in 160
	1,808 or more	One normal in 213
	1,825 or more	One normal in 286
	1,843 or more	One normal in 385
Polyuria	1,861 or more	One normal in 527
	1,879 or more	One normal in 741
	1,897 or more	One normal in 1,030
	1,915 or more	One normal in 1,450

normal person having as great or a greater deviation from the average than those represented by the tabulated volumes. It is, of course, easy to say which volumes are certainly normal and which are as certainly to be classified as oliguria or polyuria. The probability that volumes which fall in the doubtful zones belong to the normal or to the abnormal can be judged from the magnitude of the odds against any normal person giving as great or greater deviations from the average.

#### B. CONDITIONS

##### *Restriction of Water Intake, Twelve Hour Night Collections—*

The subjects were required to abstain from all fluids after breakfast until the next morning when the collection of a twelve hour night urine was completed. Under these conditions the average volume of urine

was 381 c c with a standard deviation of  $\pm 112.5$  c c and a variability of 29.5 per cent. The odds for given volumes are tabulated in Table 2. These figures are derived from ninety-four measurements on seventy-five normal adults.

## C, CONDITIONS

*Restriction of Water Intake, Urea Administration, Twelve Hour Night Collection*—The subjects took no fluids of any sort from 6 a m, except that at 6 a m and at 6 p m, 20 gm urea in 200 c c of water were taken. Urine was collected from 6 p m to 6 a m. We have thirty measurements on twenty-three normal adults. The average is

TABLE 2—DEFINITION OF OLIGURIA AND POLYURIA

Conditions    Restriction of water intake, twelve-hour night collection

Definition	Volume of Night Urine, 12 Hours, C c		Odds
Oliguria	{	21 or less	One normal in 1,450
		32 or less	One normal in 100
		43 or less	One normal in 741
		55 or less	One normal in 527
Doubtful	{	66 or less	One normal in 385
		77 or less	One normal in 286
		88 or less	One normal in 213
		100 or less	One normal in 162
		111 or less	One normal in 122
		122 or less	One normal in 93
		133 or less	One normal in 72
		144 or less	One normal in 56
Normal		381 or less	One normal in 2
Doubtful	{	617 or more	One normal in 56
		628 or more	One normal in 72
		640 or more	One normal in 93
		651 or more	One normal in 122
		662 or more	One normal in 162
		673 or more	One normal in 213
		684 or more	One normal in 286
		696 or more	One normal in 385
Polyuria	{	707 or more	One normal in 527
		718 or more	One normal in 741
		730 or more	One normal in 1,030
		741 or more	One normal in 1,450

639 c c, the standard deviation is  $\pm 153.5$  c c and the variability is 24.0 per cent. The odds for various volumes are given in Table 3.

## D, CONDITIONS

*Large Water Intake, Urea Administration, Hourly Collections at Height of Diuresis*—These collections were made under the conditions of the ratio test, which has already been described.<sup>2</sup> The largest of the three hourly volumes was taken. The average of thirty-five measurements on twenty-five normal adults was 643 c c, the standard deviation was  $\pm 88$  c c and the variability was 13.7 per cent. The odds are given in Table 4.

<sup>2</sup> Addis Arch Int Med 30:378 (Sept) 1922



TABLE 3—DEFINITION OF OLIGURIA AND POLYURIA

Conditions      Restriction of water intake, administration of urea, twelve-hour night collection

Definition	Volume, Cc	Odds
Oliguria	163 or less	One normal in 1,030
	178 or less	One normal in 740
	194 or less	One normal in 527
Doubtful	209 or less	One normal in 385
	225 or less	One normal in 286
	240 or less	One normal in 213
	255 or less	One normal in 162
	271 or less	One normal in 122
	286 or less	One normal in 93
	301 or less	One normal in 76
Normal	317 or less	One normal in 56
	639 or less	One normal in 2
Doubtful	961 or more	One normal in 56
	977 or more	One normal in 72
	992 or more	One normal in 93
	1,007 or more	One normal in 122
	1,023 or more	One normal in 162
	1,038 or more	One normal in 213
	1,053 or more	One normal in 286
Polyuria	1,069 or more	One normal in 385
	1,084 or more	One normal in 527
	1,100 or more	One normal in 741
	1,115 or more	One normal in 1,030

TABLE 4—DEFINITION OF OLIGURIA AND POLYURIA

Conditions      Large water intake, urea administration, hourly collections at height of diuresis

Definition	Volume, Cc	Odds
Oliguria	361 or less	One normal in 1,450
	370 or less	One normal in 1,030
	379 or less	One normal in 741
	388 or less	One normal in 527
Doubtful	397 or less	One normal in 385
	405 or less	One normal in 286
	414 or less	One normal in 213
	423 or less	One normal in 162
	432 or less	One normal in 122
	441 or less	One normal in 93
	449 or less	One normal in 72
Normal	458 or less	One normal in 56
	643 or less	One normal in 2
Doubtful	828 or more	One normal in 56
	837 or more	One normal in 72
	845 or more	One normal in 93
	854 or more	One normal in 122
	863 or more	One normal in 162
	871 or more	One normal in 213
	881 or more	One normal in 286
Polyuria	889 or more	One normal in 385
	898 or more	One normal in 527
	907 or more	One normal in 741
	916 or more	One normal in 1,030
	925 or more	One normal in 1,450

## II NYCTURIA

Nycturia signifies an increase in the amount of urine excreted during the night as compared with the day. Although the word has hitherto been used to denote changes in the proportion of the night volume only, there does not seem to be any good reason why it should not be employed to indicate the excretion during the night of an unusually large proportion of the solid constituents of the urine. Definitions of nycturia for urea as well as for urine volume are therefore given.

TABLE 5—DEFINITION OF NYCTURIA

Volume of urine during night as percentage of twenty-four hours volume  
Conditions Constant low water intake, urea administration

Definition	Night Volume as Percentage of 24 Hours' Volume		Odds
No nycturia	{ 33.8 or more	One normal in	2
	{ 44.98 or more	One normal in	56
	{ 45.50 or more	One normal in	72
Doubtful nycturia	{ 46.03 or more	One normal in	93
	{ 46.58 or more	One normal in	122
	{ 47.10 or more	One normal in	162
	{ 47.62 or more	One normal in	213
	{ 48.17 or more	One normal in	286
Nycturia	{ 48.70 or more	One normal in	385
	{ 49.22 or more	One normal in	527
	{ 49.75 or more	One normal in	741
	{ 50.30 or more	One normal in	1 030

TABLE 6—DEFINITION OF NYCTURIA

Urea in night as percentage of urea in twenty-four hours  
Conditions Constant low water intake, urea administration

Definition	Night Urea as Percentage of 24 Hours' Urea		Odds
No nycturia	{ 33.4 or more	One normal in	2
	{ 40.02 or more	One normal in	56
	{ 40.33 or more	One normal in	72
Doubtful nycturia	{ 40.64 or more	One normal in	93
	{ 40.96 or more	One normal in	122
	{ 41.28 or more	One normal in	162
	{ 41.91 or more	One normal in	213
	{ 41.59 or more	One normal in	286
Nycturia	{ 42.22 or more	One normal in	385
	{ 42.53 or more	One normal in	527
	{ 42.85 or more	One normal in	740
	{ 43.16 or more	One normal in	1 030

## A. CONDITIONS

*Constant Low Water Intake, Urea Administration*—The night urine was collected from 8 p. m. to 8 a. m. under the dietary conditions already given. The average percentage of urine volume and of urea to the twenty-four hour excretion was calculated for the fourth, fifth and sixth days, 20 gm. urea having been given at 8 a. m. on each of these days. There are twenty-eight observations.

The average percentage of the twenty-four hour urine volume excreted during the twelve hours of the night was 33.8 per cent, the

standard deviation was  $\pm 5.32$  per cent, and the variability was 15.7 per cent. The odds for various percentages are given in Table 5.

The average percentage of the twenty-four hour urea excreted during the night was 33.4 per cent, the standard deviation was  $\pm 3.15$  per cent, and the variability 9.4 per cent. Table 6 gives the odds.

### C. CONDITIONS

*Restriction of Water Intake, Urea Administration*—From 6 a. m. to 6 p. m. no fluids of any sort were taken, except that at 6 a. m. and at 6 p. m.

TABLE 7—DEFINITION OF NYCTURIA

Volume of night urine as percentage of twenty-four hours' urine  
Restriction of water intake, urea administration

Definition	Night Volume as Percentage of 24 Hours' Volume	Odds
No nycturia	{ 43.0 or more	One normal in 2
Doubtful nycturia	{ 53.46 or more	One normal in 56
	{ 53.95 or more	One normal in 72
	{ 54.45 or more	One normal in 93
	{ 54.95 or more	One normal in 122
	{ 55.45 or more	One normal in 162
	{ 55.95 or more	One normal in 213
	{ 56.45 or more	One normal in 286
Nycturia	{ 56.95 or more	One normal in 385
	{ 57.45 or more	One normal in 527
	{ 57.95 or more	One normal in 740
	{ 58.45 or more	One normal in 1,030

TABLE 8—DEFINITION OF NYCTURIA

Urea in night urine as percentage of urea in twenty-four hours  
Restriction of water intake, urea administration

Definition	Urea in Night Urine as Percentage of 24 Hours' Urea	Odds
No nycturia	{ 52.2 or more	One normal in 2
Doubtful nycturia	{ 62.08 or more	One normal in 56
	{ 62.55 or more	One normal in 72
	{ 63.00 or more	One normal in 93
	{ 63.48 or more	One normal in 122
	{ 63.95 or more	One normal in 162
	{ 64.42 or more	One normal in 213
	{ 64.90 or more	One normal in 286
Nycturia	{ 65.36 or more	One normal in 385
	{ 65.84 or more	One normal in 527
	{ 66.30 or more	One normal in 740
	{ 66.78 or more	One normal in 1,030

a solution containing 20 gm. urea in 200 c.c. of water was administered. There were thirty observations on twenty-three normal adults.

The average percentage of the twenty-four hour urine volume excreted during the twelve hours of the night was 43.0 per cent, the standard deviation was  $\pm 4.98$  per cent, the variability was 11.6 per cent. In Table 7 the odds are tabulated.

For the urea excretion the average was 52.2 per cent, with a standard deviation of  $\pm 4.70$  per cent and a variability of 9.0 per cent. Table 8 gives the odds.

## OBSERVATIONS ON PATIENTS WITH BRIGHT'S DISEASE

We have only scattered observations under most of the conditions outlined in the preceding section, but under both B and D conditions we have 113 volume measurements on the same group of eighty-six patients. These were an unselected, consecutively observed, group in all of whom measurement of the amount of effective renal tissue was made by means of the urea ratio test recently described. Under B conditions the patient abstains from all fluids until next morning. The night urine from 6 p. m. to 6 a. m. is collected. Under D conditions the patient is given 1,000 c. c. of water with urea at 6 a. m. and drinks 500 c. c. of water every hour thereafter until 11 a. m. The largest of three hourly collections of urine made between 9 a. m. and 12 noon is taken. The volume obtained after restriction of fluids (B conditions) will be called the minimum volume, and the largest volume after water drinking

TABLE 9—URINE VOLUMES COMPARED WITH UREA RATIOS  
113 observations on 86 Patients. Average Percentage deviations from the normal average

Diagnosis	Number of Observations	Maximum Volume Percentage	Minimum Volume Percentage	Urea Ratio Percentage
Glomerular nephritis {Diffuse	8	-64	$\pm 0$	-63
{Focal	22	-12	-16	-27
Nephrosis {Toxic	13	-15	-3	-15
{Pregnancy	8	-27	-19	-25
{Cryptic	9	-45	-13	-48
{Pyogenic	6	-83	-79	-88
Renal arteriosclerosis	32	-26	-6	-35
Renal sclerosis	15	-71	-104	-82

(D conditions) will be referred to as the maximum volume. We have thus in these patients an opportunity to compare the changes in urine volume under two diverse conditions with the changes in the amount of secreting tissue produced by the disease processes in the kidney. In Table 9 the cases have been classified in accordance with a system which will be described in a later paper. The average results of the three tests are given as  $\pm$  percentage deviations from their respective normal averages, so that they are directly comparable.

As regards the maximum volume, Table 9 shows that it is less than normal in all forms of Bright's disease. In diffuse glomerular nephritis, in pyogenic nephrosis and in renal sclerosis the deficiency is very pronounced. If the maximum volume results are compared with the urea ratio results, it will be seen that in most cases there is a marked parallelism between the degree of reduction in urine volume and the degree of reduction in the amount of effective renal tissue. These, however, are average figures. The agreement in individual cases is, of course, much less close.

With the minimum volumes a very significant abnormality is found only in pyogenic nephrosis and in renal sclerosis and in both the volumes

are larger than normal. In these two groups the degree of increase in urine volume is not dissimilar from the degree of decrease in the urea ratio, but a considerable reduction in the amount of effective renal tissue can occur without any change in minimum volume, for in diffuse glomerular nephritis with a — 63 per cent ratio the minimum volume is normal.

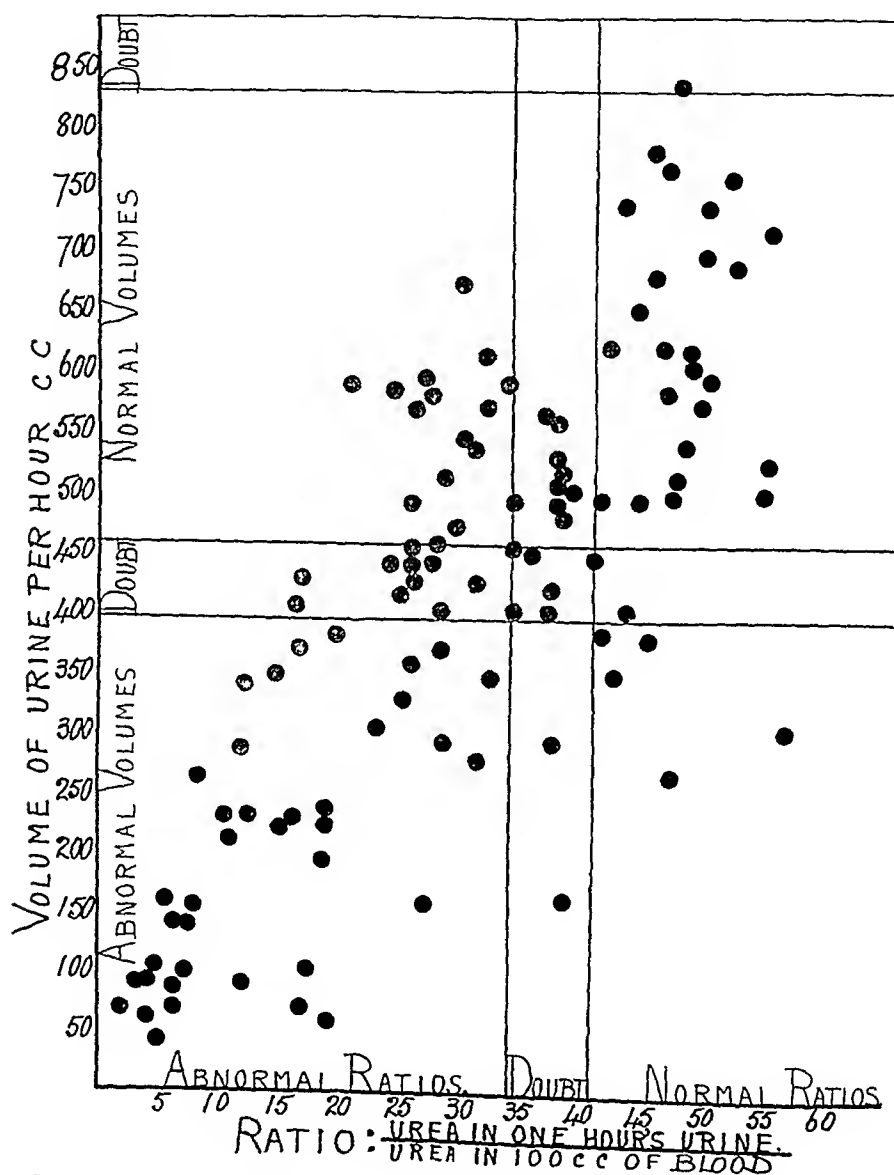


Fig 1—The relation between the maximum volume and the amount of secreting tissue in the kidney

Some idea of the individual variation in the relation between urine volume and renal tissue changes can be obtained from Figures 1 and 2. The maximum and minimum volumes are plotted on the ordinates against the urea ratios on the abscissa. In each case the limits of normal, doubtful, and abnormal values are indicated.

Figure 1 shows that some patients with normal ratios may have abnormally low maximum volumes, and also that an abnormal ratio is not necessarily associated with an abnormal volume unless the ratio is very low

Figure 2 shows that it is only in some cases with very low ratios that any definite abnormality in minimum volume is found

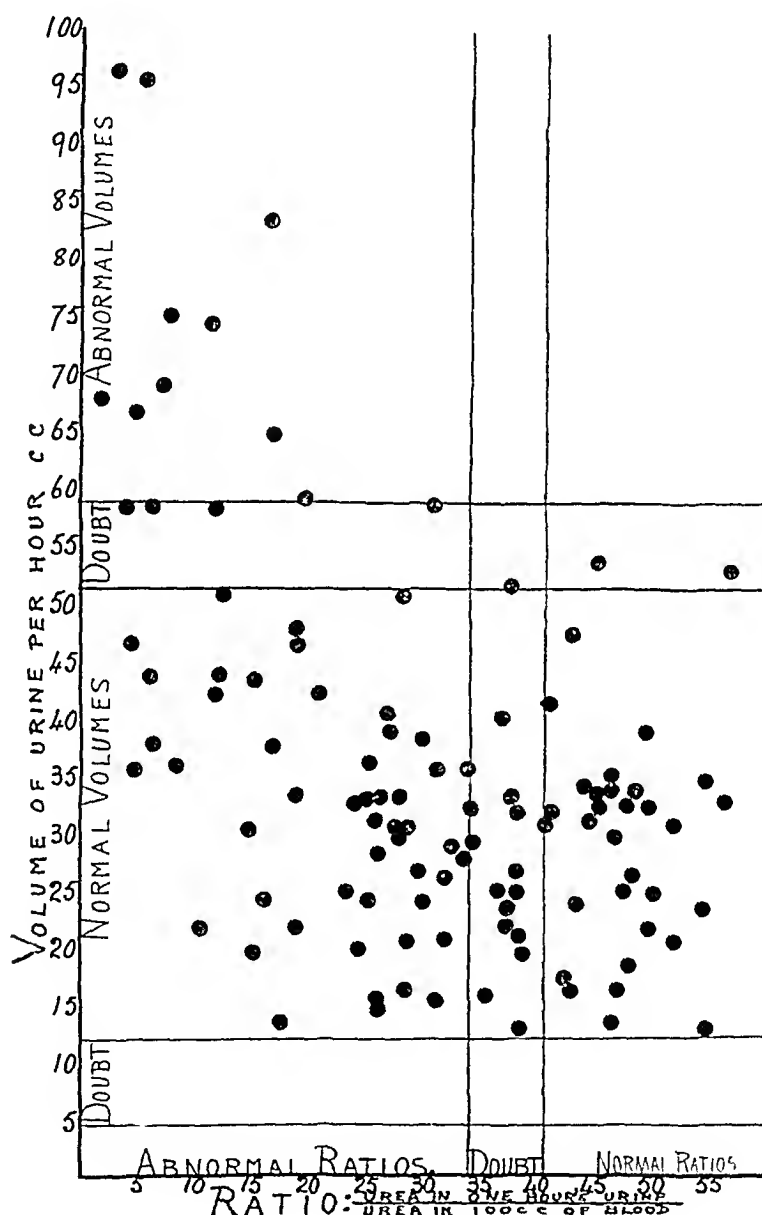


Fig 2—The relation between the minimum volume and the amount of secreting tissue in the kidney

It was not to be expected that any close relation between urine volumes and urea ratios would be found because in a large number of our patients there were many other pathologic factors than a reduction in the size of the kidney which might have had an influence on the

urine volume But all these many factors may be classified as extrarenal, and it may be said that all abnormalities in urine volume arise either from renal or from extrarenal causes or from both The recognition of any special characteristics of abnormalities of urine volume due to renal causes which would allow of their separation from volume abnormalities due to extrarenal causes, would be of clinical importance from many points of view, especially, perhaps, because such a distinction would constitute a renal test of the utmost technical simplicity since nothing more than a measurement of urine volume would be needed A consideration of the results obtained indicates that in some degree at least this distinction can be made

When a patient has a urea ratio of 10 or less, his renal secreting tissue has been so extensively rendered functionless that we may be certain that his urine volumes have been influenced by purely renal causes There is one respect in which the volume results in these low ratio cases differ from those observed in patients whose urea ratios are normal When large amounts of water are given to patients whose kidneys are very much reduced in size, their maximum volumes are shown in Figure 1 to be considerably less than normal On the other hand, when fluids are restricted, Figure 2 shows that their volumes tend to be greater than normal A reversal in the direction of the abnormality when the conditions are reversed is thus a distinctive feature of abnormalities of urine volume in which renal causes are operative The same fact is demonstrated in Table 9 The two forms of Bright's disease which have the most extreme reduction in the amount of renal tissue are pyogenic nephrosis and renal sclerosis The maximum volumes of these groups are much less and their minimum volumes much greater than the normal average

There is no such reversal of the direction of abnormality with change in the conditions in those patients whose kidneys have been only slightly, if at all, reduced in size, although such cases may show some degree of abnormality in either maximum or minimum volume Thus in some cases the maximum volume may be low because the water which is given is retained for a long time in the stomach But when the patient is given no fluids, the minimum volume is not found to be higher than normal If a patient with edema happens to be unloading the retained fluid, his minimum volume may be too great, but when he is given large quantities of water to drink, his maximum volume will not be too small, it is, in fact, often larger than usual Or, if a patient's tissues have an abnormal affinity for water, a considerable part of the water he takes may remain in his body, and his maximum volume may be too low But unless there is an advanced renal lesion, his urine volume will not be too high when fluids are restricted, on the contrary it is usually too low Under diverse conditions extrarenal

causes tend to produce abnormalities in the same direction. Renal causes produce abnormalities in opposite directions.

It follows that when renal causes produce urine volume abnormalities, the quotient obtained by dividing the maximum volume by the minimum volume will be very low. This must be so because the dividend is decreased and the divisor is increased. When extrarenal causes are operative, the change in the volume quotient is less marked because if the dividend is decreased the divisor will remain normal or be decreased, or if the divisor is increased the dividend will remain normal or be

TABLE 10—DEFINITION OF RELATION BETWEEN MAXIMUM AND MINIMUM URINE VOLUMES

The number of times by which the maximum volume exceeds the minimum volume

Definition	Maximum Volume		Odds
	Minimum	Volume	
Abnormally low	{	0.75 or less	One normal in 1 450
		1.4 or less	One normal in 1,030
		2.0 or less	One normal in 741
		2.6 or less	One normal in 527
Doubtful	{	3.2 or less	One normal in 385
		3.8 or less	One normal in 286
		4.4 or less	One normal in 213
		5.0 or less	One normal in 162
		5.6 or less	One normal in 122
		6.2 or less	One normal in 93
		6.8 or less	One normal in 72
Normal	{	7.4 or less	One normal in 56
		20.2 or less	One normal in 2
Doubtful	{	33.0 or more	One normal in 56
		33.6 or more	One normal in 72
		34.2 or more	One normal in 93
		34.8 or more	One normal in 122
		35.4 or more	One normal in 162
		36.0 or more	One normal in 213
		36.6 or more	One normal in 286
Abnormally high	{	37.2 or more	One normal in 385
		37.9 or more	One normal in 527
		38.4 or more	One normal in 741
		39.1 or more	One normal in 1,030
		39.7 or more	One normal in 1 450

increased. There is, therefore, good reason to believe that what we may call the volume quotient will be of value in distinguishing between renal and extrarenal causes of urine volume abnormalities.

Unfortunately, we do not have an adequate standard of normality for the volume quotient. Our standards for maximum and minimum volumes were obtained at different times on separate groups of normals, and since then we have been able to collect only thirty-two observations on thirty-one subjects. This is inadequate because the quotient necessarily carries the variability of both divisor and dividend and a considerably larger number of observations should have been made. The average quotient was found to be 20.2 with a standard deviation of  $\pm 6.08$  and a variability of  $\pm 30.2$  per cent. The odds for various quotients are given in Table 10.



In Figure 3 the quotients of individual patients are plotted against the results of the urea-ratio test. No patients with normal ratios have abnormal quotients and no patients with a ratio of 10 or less have normal quotients.

The principle on which the volume quotient test is based is, I believe, a sound one, but it seems likely that the conditions used in carrying it

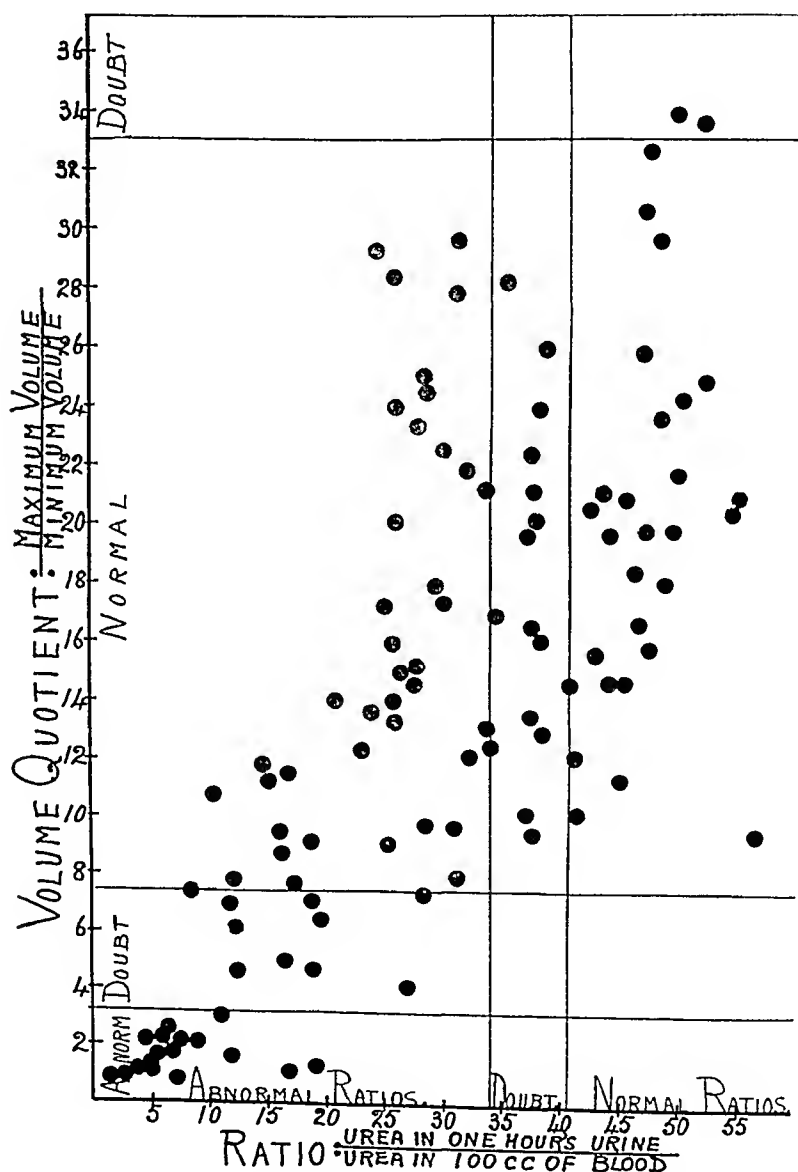


Fig 3—The relation between the volume quotient, i e,  $\frac{\text{maximum volume}}{\text{minimum volume}}$  and the amount of secreting tissue in the kidney

out can be improved. This is the main reason why a more reliable standard of normality was not obtained. The normal "minimum" volume, especially, is highly variable and rarely approaches the true minimum. The variability is probably due, in the main, to differences

in the amount of "stored" water in the tissues of normal persons so that even after fluid restriction the night urine has still, in some cases, a considerable volume. If abstention from fluids were continued until the appearance of some such evidence of excess water depletion as a pronounced thirst, the volumes would probably be more constant and closer to the true minimum. But there are practical difficulties in that direction. The night urine is convenient and has a volume so considerable that errors from incomplete emptying of the bladder are probably not large. Certainly no short time collections would be feasible after fluid restriction. We are trying to find conditions which will combine convenience with a greater degree of strain and greater uniformity than our present method imposes. A properly conditioned volume quotient would be a useful renal test because it would have no technical difficulties of measurement and would in some degree free the physician from dependence on the laboratory.

There does not, however, seem to be any present prospect of a quantitatively accurate renal test based on urine volume measurements alone. It is true that water can be ingested in much larger quantities than can any other substance, and if it were possible to get so large an amount into the blood that the water excreting capacity of the kidneys were overtaxed, we might expect to find a direct relationship between the amount of secreting renal tissue and the magnitude of the volume of urine excreted during a given time. But experiments with rabbits have convinced us that the renal capacity cannot be overtaxed by any amount of water it is at all practical to administer. We are thus obliged to measure the amount of water in the blood. But even when a pronounced diuresis has been induced by water drinking, the increase in the total water content of the blood is slight. This fact has been reemphasized by Haldane and Priestley<sup>3</sup> and we have made the same observation. It is only that relatively small part of the total water of the blood which is available for excretion by the kidney which should be measured, but we have no means of determining the amount of this fraction alone. Until such a method has been developed, it is not possible to determine the ratio between the water in the urine and the free water in the blood, the figure which, if it were obtained under appropriate conditions, would probably give the most accurate indication of the water excreting capacity of the kidneys and would bear the closest relation to the amount of renal secreting tissue.

#### CONCLUSIONS

1 The terms oliguria, polyuria and nycturia have been statistically defined by reference to the distribution of urine volumes and of urea

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3 Haldane and Priestley *J. Physiol.* 50 296, 1916

excretion found in normal adult subjects under fixed conditions designed to put a strain on the water and urea excreting capacity of the kidney

The following distributions were found ,

#### OLIGURIA AND POLYURIA

Conditions	Average Cubic Centimeters	Standard Deviation Cubic Centimeters	Variability Per Cent
A	1345	$\pm 178.0$	13.2
B	381	$\pm 112.5$	29.5
C	639	$\pm 153.5$	24.0
D	643	$\pm 88$	13.7

#### NYCTURIA

##### 1 Volume of Urine

Conditions	Average Per Cent	Standard Deviation Per Cent	Variability Per Cent
A	33.8	$\pm 5.32$	15.7
C	43.0	$\pm 4.98$	11.6

##### 2 UREA

Conditions	Average Per Cent	Standard Deviation Per Cent	Variability Per Cent
A	33.4	$\pm 3.15$	9.4
C	52.2	$\pm 4.70$	9.0

2 Abnormalities in urine volume which are due to renal causes are characterized by the fact that with a large intake of water the volumes are too small, while with a small intake of water the volumes are too large. Extrarenal causes do not produce this reversal of the direction of abnormality when the conditions are changed.

3 In those cases in which renal causes of urine volume abnormality are predominant, the quotient obtained by dividing the volume per hour when a large amount of water has been taken by the volume per hour when fluids are restricted is much less than the normal average, whereas, when extrarenal causes are operative, the quotient deviates to a lesser degree, if at all, from the normal.

# STUDIES ON THE PHYSIOLOGY OF THE LIVER

## IV THE EFFECT OF TOTAL REMOVAL OF THE LIVER AFTER PANCREATECTOMY ON THE BLOOD SUGAR LEVEL<sup>\*</sup>

FRANK C MANN, M D, AND THOMAS B MAGATH, M D

ROCHLSTLR, MINN

Previous reported studies<sup>1</sup> on the physiology of the liver have demonstrated that (1) a characteristic group of symptoms followed by death develops after total removal of the liver, (2) these symptoms are associated with decreasing blood sugar, and the various symptoms and death occur at definite blood sugar levels, (3) the injection of glucose after symptoms develop abolishes them and restores the animal to normal, and (4) if glucose is administered after hepatectomy in amounts sufficient to maintain the blood sugar level at normal or above normal, the characteristic symptoms do not develop, but the animal lives for a variable period of time, which is always much longer than if glucose had not been administered, and dies following the development of a totally different group of symptoms

These striking and very definite results have proved that the maintenance of the normal level of blood sugar is absolutely dependent on the liver. Furthermore, there is a certain critical level of blood sugar below which it is impossible for the organism to live. The liver thus assumes renewed importance and undoubtedly has a vital function as regards carbohydrate metabolism

Since the classical experiments of Mering and Minkowski<sup>2</sup> it has been known that total pancreatectomy produces glycosuria. Many investigators have demonstrated that hyperglycemia follows total removal of the pancreas. This effect has been attributed to an internal secretion of the island tissue of the organ. The experiments of Banting and Best,<sup>3</sup> working in MacLeod's laboratory, have greatly strengthened this internal secretion theory

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<sup>\*</sup> From the Division of Experimental Surgery and Pathology, and the Section on Clinical Laboratories, The Mayo Foundation

1 Mann, F C, and Magath, T B. Studies on the Physiology of the Liver. II The Effect of the Removal of the Liver on the Blood Sugar Level, *Arch Int Med* **30** 73-84 (July) 1922. Studies on the Physiology of the Liver. III The Effect of Administration of Glucose in the Condition Following Total Extirpation of the Liver, *Arch Int Med* **30** 171-181 (Aug) 1922.

2 Mering, J, and Minkowski, O. Diabetes mellitus nach Pankreasextirpation, *Arch f exper Path u Pharmacol* **26** 371-387, 1889.

3 Banting, F G, and Best, C H. The Internal Secretion of the Pancreas, *J Lab & Clin M* **7** 251-266, 1922. Pancreatic Extracts, *J Lab & Clin M* **7** 464-472, 1922.



hepatectomy in mammals (Bock and Hoffman,<sup>4</sup> Schenck,<sup>5</sup> Tangl and Harley<sup>6</sup>) has a bearing on the problem only as regards the fact that the technic which they employed in removing the liver in many instances must have also greatly damaged the circulation to the pancreas. In those experiments in which the circulation was restricted to the anterior portion of the body (Seegen,<sup>7</sup> Kaufmann<sup>8</sup>) both the liver and pancreas were functionally removed. In the experiments in which

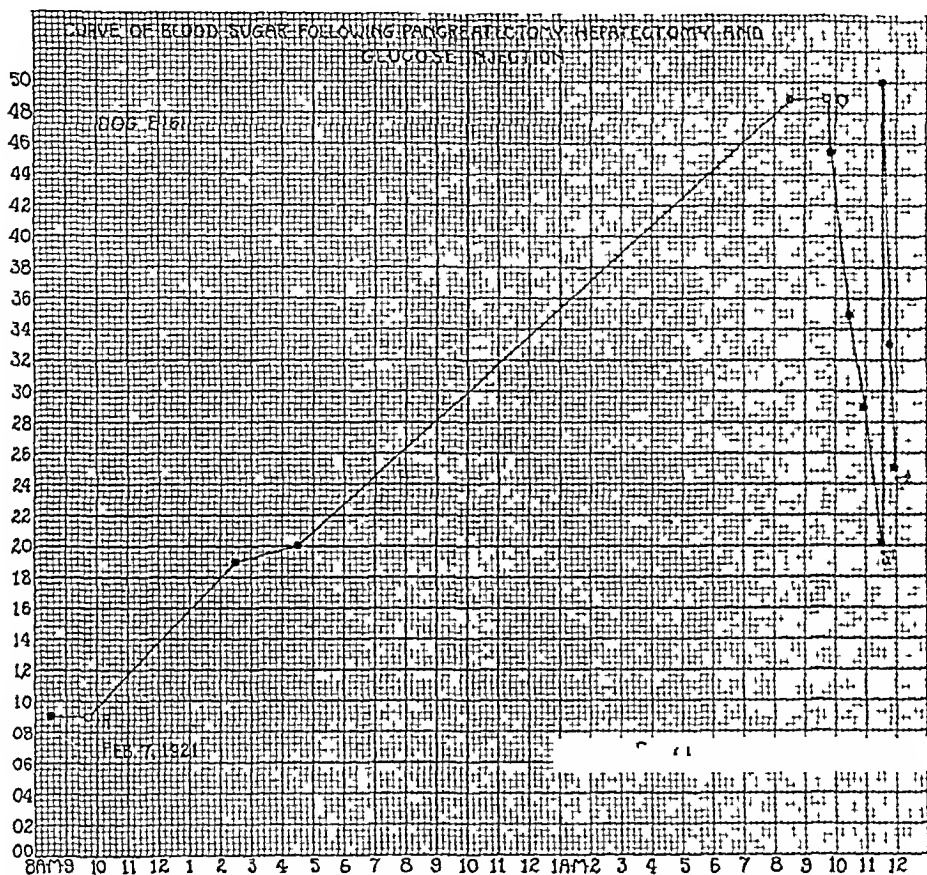


Fig 2—R, pancreas removed O (forty-eight hours later), liver removed, S, characteristic symptoms. An injection of glucose was given. The animal was restored to normal for a short time but at S<sup>2</sup> symptoms again appeared. Note the increase in blood sugar following pancreatectomy, the subsequent decrease following hepatectomy and the development of symptoms with a blood sugar above normal.

4 Bock, C, and Hoffmann, F. A. *Experimental Studien über Diabetes*. Berlin, H. E. Olven, 1874.

5 Schenck, F. *Ueber den Zuckergehalt des Blutes nach Blutentziehung*. *Arch f d ges Physiol* **57** 553-572, 1894.

6 Tangl, F, and Harley, V. *Beitrag zur Physiologie des Blutzuckers*. *Arch f d ges Physiol* **61** 551-559, 1895.

7 Seegen, J. *Die Zuckerbildung im Thierkörper, ihr Umfang und ihre Bedeutung*. Berlin, A. Hirschwald, 1890.

8 Kaufmann, M. *Nouvelles recherches sur la pathogenie du diabète pancreatique*. *Compt rend Acad d sc* **118** 656-659, 1894.

evisceration was employed, (Kaufmann,<sup>9</sup> Pavy and Siau<sup>10</sup>), the pancreas might or might not have been damaged. It is obvious that such experiments are necessarily very short and offer no opportunity to note symptoms and make other observations. It should be noted, however, that in all of these experiments a decrease in blood sugar was found.

Hedon<sup>11</sup> seems to have been the first to remove the liver from dogs after previously performing pancreatectomy. His results are inconclusive.

Kaufmann<sup>9</sup> removed different portions of the viscera in normal and pancreatectomized dogs and observed the blood sugar. He was not successful in removing the entire liver and the animals were maintained

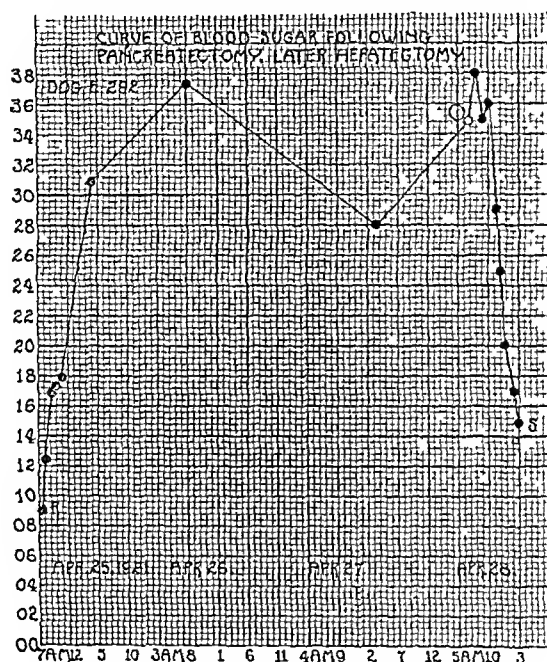


Fig 3—Curve of blood sugar following pancreatectomy, later hepatectomy R, pancreas removed, O (seventy-two hours later), liver removed S, characteristic symptoms

under chloroform anesthesia. He records a decrease in blood sugar in both normal and pancreatectomized animals.

Marcuse<sup>12</sup> removed the pancreas from frogs and noted a marked glycosuria. He then removed the pancreas and liver simultaneously from the same species of animal and no glycosuria was observed.

9 Kaufmann, M. De l'influence exercee par la suppression partielle ou totale de la fonction hepatique sur la glycemie chez les animaux normaux et diabetiques. *Arch de physiol norm et path* 8 151, 1896.

10 Pavy, F. W., and Siau, R. L. The Influence of Ablation of the Liver on the Sugar Content of the Blood, *J. Physiol* 29 375-381, 1903.

11 Hedon, E. Sur la pathogenie du diabete consecutif à l'extirpation du pancreas. *Arch de physiol norm et path* 4 245-258, 1892.

12 Marcuse W. Ueber die Bedeutung der Leber für das Zustandekommen des Pankreas-diabetes. *Ztschr f klin Med* 26 225-257 1894.

Kausch<sup>13</sup> has made the most extensive investigation of the blood sugar following removal of both the liver and pancreas. He employed geese and ducks. He first removed the liver of a series of normal fowls in a manner similar to Minkowski,<sup>14</sup> and obtained identical results with respect to symptoms and decrease in blood sugar following hepatectomy. He then removed the liver from fowls from which the pancreas had been removed from twelve to forty-eight hours previously. He found that the blood sugar decreased even more rapidly in the fowls which had been pancreatectomized preceding the hepatectomy. He also noted that the pancreatectomized birds had less glycogen in the muscle than the normal controls and considers this decrease in the reserve

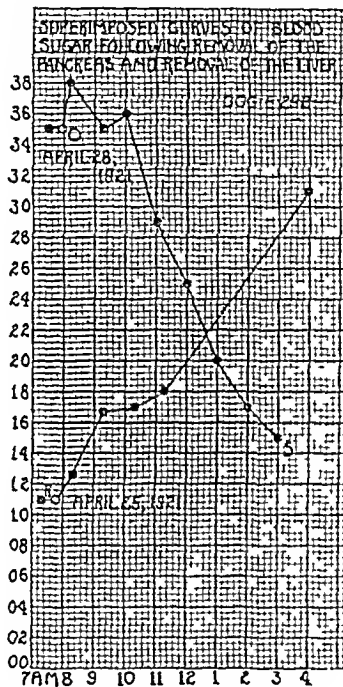


Fig 4—This curve is composed of the two portions of the curve in Figure 3, in order to illustrate the reciprocal action of the liver and pancreas as regards blood sugar. The removal of the pancreas, R, produces an immediate increase in blood sugar, while removal of the liver produces an equally characteristic decrease.

supply of carbohydrate the cause for the more precipitate decrease in blood sugar when both glands were removed.

MacLeod and Pearce<sup>15</sup> studied the results of disappearance of sugar in eviscerated dogs, normal animals and those previously pancrea-

13 Kausch, W. Der Zuckerverbrauch im Diabetes mellitus des Vogels nach Pankreasextirpation, Arch f exper Path u Pharmacol **39** 219-244, 1897.

14 Minkowski, O. Ueber den Einfluss der Leberextirpation auf den Stoffwechsel, Arch f exper Path u Pharmacol **21** 41-87 1886.

15 Macleod, J. J. R., and Pearce, R. G. The Sugar Consumption in Normal and Diabetic (Depancreated) Dogs After Evisceration. Am J Physiol **32** 184-199, 1913. Further Observations on the Rate at Which Sugar Disappears from the Blood of Eviscerated Animals. Am J Physiol **33** 378-381 1914.



tectomized While their results were quite variable, they obtained a decrease in blood sugar in both series of experiments It should be noted that such experiments necessarily require the continuous use of anesthetics or other means of maintaining unconsciousness

A survey of the previous work on the blood sugar level following removal of both liver and pancreas shows that a decrease has almost invariably occurred However, with the exception of the experiments on ducks and geese in which the portal system anastomoses with the systemic venous system, the results of the experiments were not conclusive

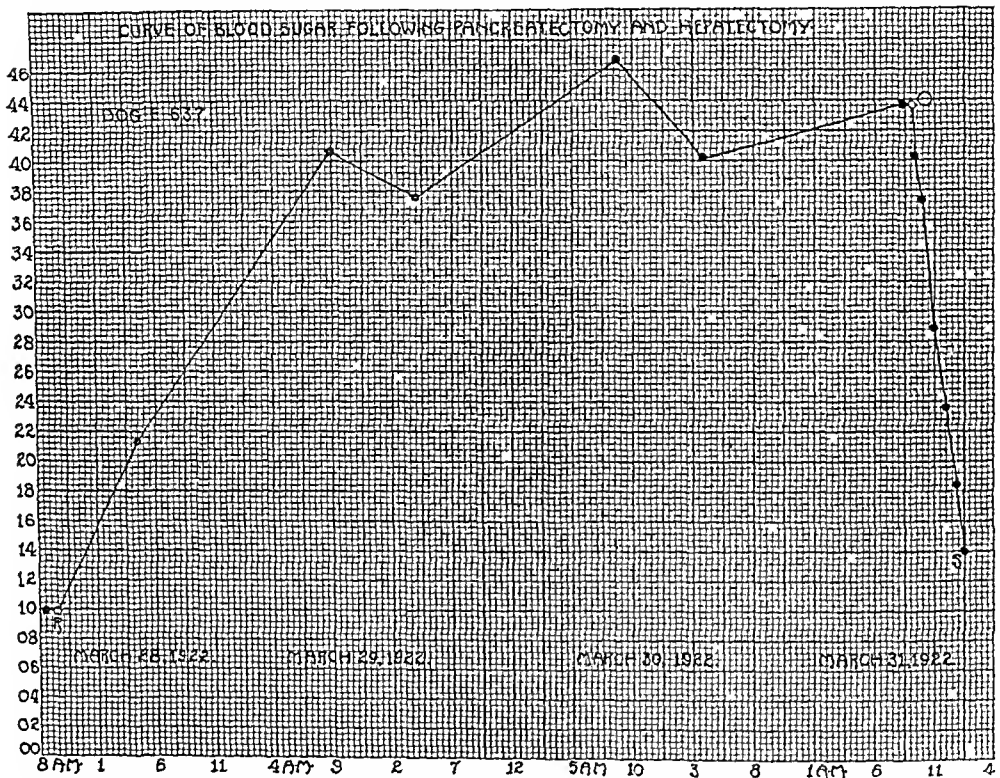


Fig 5—Curve of blood sugar following pancreatectomy and hepatectomy R, pancreas removed, O (ninety-six hours later), liver removed S, characteristic symptoms developed

#### METHOD OF EXPERIMENTATION

All of our operations were performed under ether anesthesia and with sterile technic The animals (dogs) were prepared for removal of the liver by the two preliminary operations previously described The pancreas was then removed, employing the usual technic At varying periods of time after pancreatectomy the liver was removed The blood sugar was estimated at varying intervals throughout the experiment After pancreatectomy the animals were given a milk diet The methods employed for obtaining blood specimens and estimation of blood sugar were the same as those previously described

*Total Removal of the Liver and Pancreas at the Same Time—*

When the pancreas and liver are removed at the same operation the resultant condition is the same as though only the liver had been removed. The blood sugar decreases, and associated with this decrease, the characteristic symptoms which follow hepatectomy develop. The curve of blood sugar is the same as when the liver alone is removed. The injection of glucose restores the animal to normal. Usually the animal does not live as long after operation as when only the liver is removed, but otherwise the pancreatectomy does not seem to exert any effect on the resulting condition.

*Total Removal of the Liver from Twenty-Four to Forty-Eight Hours After Pancreatectomy—*The blood sugar level is usually from two to four times greater than normal, from twenty-four to forty-eight hours after total pancreatectomy. When the liver is removed at this time the decrease in blood sugar takes place immediately and is

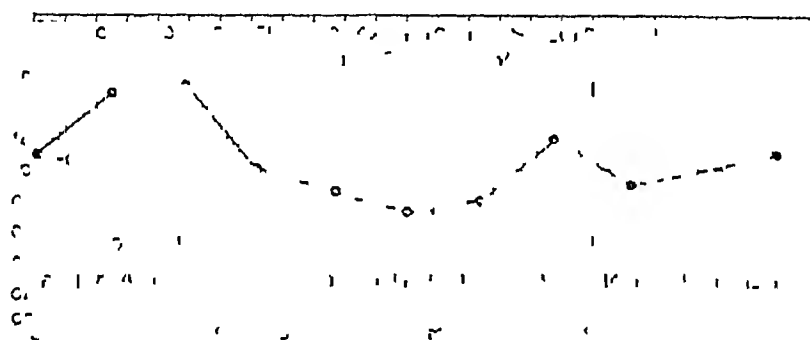


Fig 6—Curve of blood sugar following total pancreatectomy and partial hepatectomy. This curve is a continuation of the curve given in Figure 7. At R-O the pancreas and approximately 40 per cent of the liver were removed. Note that the blood sugar remained almost normal during the succeeding days although the animal was on a milk diet and developed the other characteristics of a pancreatectomized animal.

most marked. The characteristic symptoms associated with hepatectomy develop, but they appear earlier than if only the liver has been removed and usually appear at a much higher blood sugar level. The animal is restored to normal by the injection of glucose, but it soon develops symptoms again and dies within a few hours after removal of the liver.

*Total Removal of the Liver from Forty-Eight to Ninety-Six Hours After Pancreatectomy—*The blood sugar level usually remains fairly constant at from four to five times above normal from forty-eight to ninety-six hours after total removal of the pancreas. When the liver is removed during this interval, following pancreatectomy the decrease in blood sugar takes place immediately and is most marked. Within two hours after hepatectomy the characteristic symptoms appear but

they develop at a blood sugar level which, although considerably below the preoperative level, is still above normal. The injection of glucose produces a fleeting restorative reaction but the animal soon passes into coma and dies.

*Total Removal of the Liver More than Ninety-Six Hours After Pancreatectomy*—Coma has followed the anesthesia and operative procedure of hepatectomy in all animals in which the liver was removed more than ninety-six hours after total pancreatectomy.

*Partial Removal of the Liver Before and After Pancreatectomy*—As our results indicated that the hyperglycemia following pancreatectomy was dependent on the presence of the liver, it seemed desirable

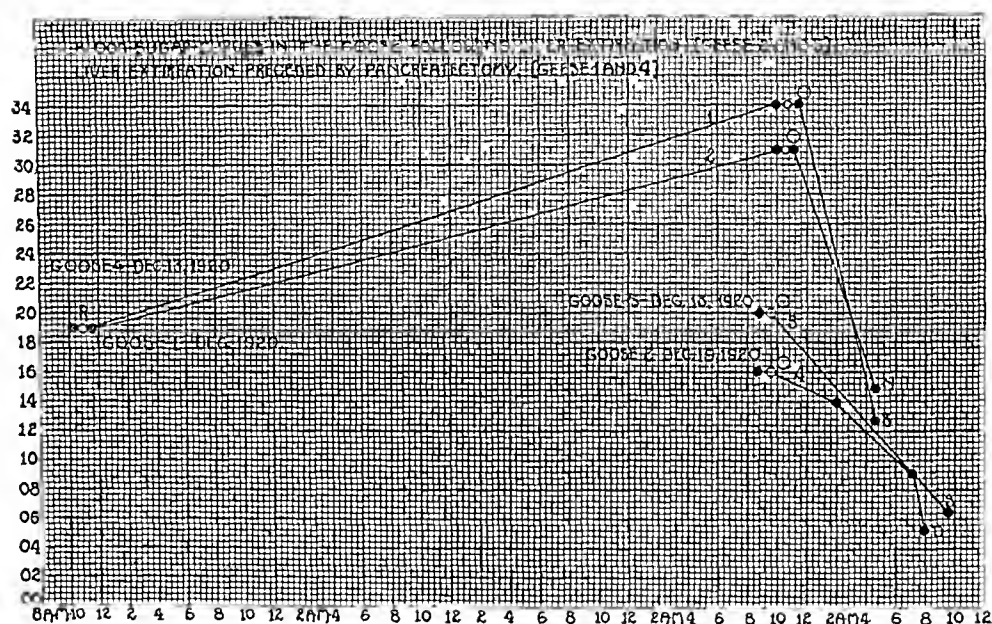


Fig 9—R, pancreas removed, O, liver removed, N, normal, S characteristic symptoms, D, fowl died

to determine whether a partial removal of the liver would affect the change in blood sugar level following pancreatectomy. In the first experiments we removed the pancreas from normal dogs, and a few days later, when a marked hyperglycemia had developed, various portions of the liver were removed. Subsequent to the partial hepatectomy the blood sugar decreased but did not return to a normal level. The totally pancreatectomized animal did not withstand the subsequent operation well and the results of the experiments were inconclusive. In the next series of experiments portions of the liver were removed at the same time as the pancreas. The hyperglycemia resulting from the pancreatectomy was not so great, but otherwise the same results were noted as when the liver was left intact.

It has been emphasized by our previous experiments and those of other investigators, that only a small portion of the normal liver is necessary for the maintenance of its function. In a previous article<sup>16</sup> we reported a method for producing chronic insufficiency of the liver. Briefly, the method consists in removing a portion of the liver of an animal in which an Eck fistula has been made a considerable time before. Such a liver does not seem capable of regenerating to any great extent and consequently its function can be greatly reduced.

We, therefore, tried removing the pancreas and a portion of the liver from an animal in which an Eck fistula had been made several weeks before. Total removal of the pancreas and partial removal of the liver in such an animal does not produce marked changes in blood sugar. In fact, in one animal the blood sugar remained within normal limits for ten days after operation and there was no glycosuria, although the animal exhibited the general appearance of having been pancreatectomized.

#### DISCUSSION

The results of the experiments are very definite as regards the liver, and their interpretation seems evident. They prove conclusively that the liver is absolutely necessary for the maintenance of the blood sugar level in the hyperglycemic animal in the same manner as in the normal animal. The increase in blood sugar following pancreatectomy is dependent on the presence of the liver. Without an adequate amount of functioning liver tissue, the increase in blood sugar following pancreatectomy could not occur. We have thus proved in another way that whatever may be the process of carbohydrate metabolism, the liver has a vital part in that process.

The results of the experiment with regard to the pancreas are not so clear. They do not show why the loss of the pancreas should cause the rise in the blood sugar, but they do prove that the presence of the liver is necessary for this rise. It is evident that the decrease in blood sugar in the pancreatectomized animal following hepatectomy is due to the total loss of the mechanism for supplying this sugar, but what becomes of the sugar in the blood of the pancreatectomized and hepatectomized animal if it is not utilized is not so evident. The sugar was not eliminated by way of the kidneys because many of the animals were anuric after hepatectomy, and those that did secrete urine passed only a small amount of sugar after operation. It is possible but not probable, that enough of the internal secretion of the pancreas was present after pancreatectomy to account for the decrease after hepa-

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16 Mann, F. C. and Magath, T. B. The Production of Chronic Liver Insufficiency. *Proc. Am. J. Physiol.* 59:485, 1922.

tectomy Another point of interest is the observation that the characteristic symptoms following hepatectomy occur at a much higher blood sugar level when the pancreas has been removed some time before

#### SUMMARY

The liver and pancreas were removed at varying intervals in relation to each other When the two glands were removed at the same time, the resulting condition was the same as though only the liver had been removed When the liver was removed from twenty-four to ninety-six hours after pancreatectomy, the blood sugar decreased quickly and the same characteristic symptoms developed as after hepatectomy, but at a higher blood sugar level The injection of glucose restored the animal to a normal state, but the effect of the glucose was transitory The total removal of the pancreas and partial removal of the liver in an animal in which an Eck fistula had been made was followed by only slight or no increase in blood sugar These experiments prove that the presence of the liver is absolutely necessary for the hyperglycemia following pancreatectomy

# THE PRODUCTION OF URINARY CALCULI BY THE DEVITALIZATION AND INFECTION OF TEETH IN DOGS WITH STREPTOCOCCI FROM CASES OF NEPHROLITHIASIS

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Infection is regarded as a common cause of calcification in tissues, but the hypothesis that certain microorganisms which infect man may have peculiar power in this respect is not generally believed. It was suggested to one of us during experiments with a streptococcus isolated from an excised piece of muscle in a case of calcifying myositis. This strain was peculiar, in comparison with strains of streptococci from the more common forms of myositis, in that it not only produced marked lesions in the muscles of rabbits when injected intravenously, but also produced very early precipitation of calcium salts in the lesions<sup>1</sup>. The etiologic relationship of streptococci to the formation of gallstones was demonstrated by one of us a number of years ago in experimental cholecystitis produced by intravenous injection of streptococci from cholecystitis in man<sup>2</sup>.

During the preparation of immune serums, in which repeated intravenous injections of dead streptococci having different localizing powers were made, numerous concretions were found at necropsy in the calices and substance of the kidneys (Fig 1) of the sheep injected with a pyelonephritis strain, no other lesions were found.

In a series of experiments in which nephritis followed the devitalization and infection of teeth in dogs with a staphylococcus from a case of nephritis, one dog developed pyelitis and cystitis, with marked calcareous deposits in the adherent exudate in the pelvis of the kidney and in the bladder<sup>3</sup>.

On the basis of these observations it was believed to be worth while to attempt to produce urinary calculi in dogs by creating foci of infection around the teeth with organisms isolated from the urine and foci of infection in persons suffering from nephrolithiasis, thus simulating the conditions so often present in patients. In this paper we shall report the results obtained in a series of experiments with the streptococci

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\* From the Division of Experimental Bacteriology, The Mayo Foundation

1 Rosenow, E C, and Ashby, Winifred. Focal Infection and Elective Localization in the Etiology of Myositis, *Arch Int Med* **28** 274 (Aug) 1921

2 Rosenow, E C. The Etiology of Cholecystitis and Gallstones and Their Production by the Intravenous Injection of Bacteria, *J Infect Dis* **19** 527, 1916

3 Rosenow, E C, and Meisser, J G. Elective Localization of Bacteria Following Various Methods of Inoculation and the Production of Nephritis by Devitalization and Infection of Teeth in Dogs, *J Lab & Clin M* **7** 707, 1922

isolated from typical examples of this disease, a study made possible through the cooperation of Dr Braasch and his associates, of the section on urology in the Mayo Clinic

#### METHOD OF STUDY

Cultures from the catheterized urine of the patients and from foci of infection in tonsils and teeth were made on blood-agar and in tall tubes of glucose-brain broth. The primary culture in glucose-brain broth, containing a pure growth or a preponderance of the streptococci, was usually first inoculated intravenously into rabbits. If lesions of the urinary tract, usually of the medulla of the kidneys, developed, from which the streptococcus could be isolated, the teeth of dogs were inoculated with this strain. In some instances the teeth of dogs were



Fig 1—Photograph of a colored drawing of the kidney of a sheep showing concretions following repeated intravenous injections of a dead streptococcus from pyelonephritis ( $\times \frac{3}{4}$ )

infected with the primary culture directly from the foci of infection or from the urine of the patient

The dogs selected were active and well nourished. Catheterized specimens of urine were normal, and roentgenograms of the kidneys, ureter and bladder were negative at the beginning of the experiments. In devitalizing and infecting the teeth, the animals were covered with a sterile sheet, and kept under ether anesthesia by the intratracheal method. A rubber dam was used to isolate the teeth to be worked on. The teeth were scrubbed, and sterilized with alcohol and tincture of iodine, then cut off with sterile bone nippers midway between the incisal edge and the gum margin. The pulp canal was drilled into with sterile dental drills. The pulps were removed with sterile broaches, and after the hemorrhage had ceased, the bacteria, in dense suspension, were introduced into the pulp chambers with fine capillary glass pipets. The canals

were then sealed with impervious dental cement or amalgam. In most instances three cuspids were infected, in a few cases, only the two lower cuspids were infected, and in order to determine whether the streptococci from these artificially produced foci, or bacteria from other sources might localize and produce periapical infection around teeth from which the pulp had been removed, the fourth cuspid was devitalized, but not infected. The animals were numbered and weighed, they were kept under hygienic conditions and fed a balanced ration of dog biscuit, occasionally supplemented by meat. A supply of water rich in lime salts was constantly before them. Catheterized specimens of urine were examined at intervals. In from fifty-one to 120 days after the infection of the teeth, one kidney was removed from each dog by Dr. Williamson. This afforded opportunity at necropsy some time later to compare the findings in that kidney with those of the opposite kidney.

Various tests were made to prove the causal relationship of the streptococci in the experimentally induced foci of infection to the lesions in the urinary tract and the formation of renal calculi. Cultures were made from the infected teeth, urine, kidneys and renal calculi in the dogs. The localizing power of the freshly isolated cultures was determined by intravenous injection into rabbits. Painstaking search was made for the organism in the lesions in the kidneys and in, or adjacent to, areas in which sections revealed beginning stone formation.

In studying the localizing power of the strains isolated from the patients and from the dogs whose teeth were infected, from 3 to 5 c.c. of the primary culture in glucose-brain broth was injected intravenously into rabbits of medium size. In some instances young cultures in the second to the fourth rapidly made subculture were injected. Search for focal lesions of the viscera, including the medulla of the kidney, was made immediately in the animals anesthetized for examination in from two to seven days after injection, and as soon after death as possible in those animals that died as the result of the injection. The urine was cultured and examined for albumin, casts, pus and blood. Cultures from the kidneys of the dogs and rabbits were usually made from small amounts of the pipetted substance of the kidney, occasionally from large portions macerated in a mortar, from the teeth with the pipetted material from the pulp chamber and infected area in the periapical region, and from the crushed calculi after repeated washings in sterile salt solution. The tissues were fixed in 10 per cent formaldehyd solution and imbedded in paraffin. Sections were stained for lesions with hematoxylin and eosin, for bacteria by the Gram method, and treated by von Kossa's silver nitrate method to prove that the deposits in the kidneys which stained deeply with hematoxylin contained lime salts.



Nine cases of nephrolithiasis were studied. In order best to illustrate the results obtained, we shall give detailed experiments in the first case studied, and a summary of the results of all the cases.

### HISTORY OF CASE

*History*—A physician, aged 34 years, had repeated attacks of renal colic for four years previous to our investigation. The first attack occurred about six months after an attack of pansinusitis, in which there was marked prostration, fever and pain for three weeks, followed by slow recovery. For several years the attacks of colic occurred only during the cold months, and at first were thought to be due to gallstones, but later they proved to be due to stones in the right kidney. In the autumn of 1918, six months after his attack of sinusitis, a rough stone, somewhat larger than a wheat grain, was passed. This was followed by hematuria and the passage of blood clots, and at times dull pain in the right loin, and abdomen, but there was no colic for twenty-three months. October, 1920, after heavy lifting, he had an attack of marked weakness, followed by hematuria. The hematuria recurred for two days, and for six weeks he had many attacks of severe colic.

*Examination*—Cystoscopic and roentgen-ray examinations revealed an impacted stone in the right ureter, 10 cm from the bladder.

*Treatment*—This calculus was removed by Dr Judd Nov 27, 1920. The stone was extremely hard and consisted largely of calcium carbonate. Convalescence was uneventful and the patient was free from renal symptoms for three months, when they recurred. In March, 1921, he passed five soft stones. He then had intermittent attacks for several months. September 28, he had severe colic, followed by chills and fever.

From June 23 to August 5, 1921, the patient was given seven subcutaneous injections of a lipovaccine prepared from the strain of streptococcus that was inoculated into the teeth of the dogs. The dose varied from 340 to 960 millions of streptococci. He had no constitutional reaction, and there was no change in the number and severity of attacks.

From Nov 10, 1920, to Oct 21, 1921, six infected teeth were removed in four sittings. All of these had been rendered pulpless some years before. One tooth which gave symptoms of a dying pulp, was removed by simple extraction Oct 21, 1921. Severe constitutional reaction followed within five hours and lasted for several days. Our experiments were performed with cultures from this tooth.

Lavage of the kidneys, prolonged rest and forced feeding, especially with large quantities of milk, were instituted after extraction of the last infected tooth. During six weeks the patient gained twenty pounds, and remained free from urinary symptoms until June 1, 1922, when, after a long automobile trip, he developed pain and tenderness around the teeth in the upper jaw on the left side, the result of acute infection of the left antrum. During this attack the patient developed colic and hematuria, but was not aware of passing a stone. After the acute symptoms had subsided, the antrum was irrigated on two occasions, the urine was kept neutral or alkaline by the administration of sodium bicarbonate for several months and the patient was free from urinary symptoms for five months.

*Bacteriologic Examination*—During the attacks of colic the urine usually contained pus, gross or microscopic blood, relatively few casts, and a small amount of albumin. In quiescent intervals only a few leukocytes were found out during attacks many were found, and always a moderate increase in the amount of mucus. Smears from the sediment and from the flakes of mucus yielded short-chained streptococci and staphylococci. Blood-agar-plate cultures from the sediment of catheterized and staphylococci. Blood-agar-plate cultures yielded a variable number of small dry usually nonadherent colonies.

of streptococci, surrounded by a narrow greenish zone, often with slight hemolysis peripheral to this zone, and a small number of larger, opaque, grayish, indifferent colonies of staphylococci. The growth in glucose-brain broth was usually granular, often with spontaneous precipitation in from twenty-four to forty-eight hours. Smears yielded long and short chains of elongated, nonencapsulated, gram-positive diplococci, varying considerably in size. Blood-agar plate cultures from the broth, and directly from the urine, yielded the two types of colonies described, the green colonies of streptococci always predominating in number. The morphology of the organisms, and the colonies on blood-agar resembled *Streptococcus viridans*. At times it was difficult to differentiate the staphylococci from isolated diplococci, or from diplococci in clumps. Moreover, large and small coccus forms occurred in chains consisting otherwise of typical elongated diplococci.

#### EXPERIMENTAL OBSERVATIONS

The primary culture in glucose-brain broth from the tooth extracted Oct. 21, 1921, following which the patient had a reaction, was injected into four rabbits. All appeared well forty-eight hours after the injection, when they were anesthetized. All had mild lesions in the kidneys, chiefly of the medulla, and two also had hemorrhages of the bladder, but were otherwise free from lesions. A small amount of albumin, blood and pus cells was found in the urine of three rabbits. The culture of a lymphoid tag from a tonsillectomy scar produced lesions in the medulla of the kidneys of two rabbits injected intravenously, in one rabbit, hemorrhages and infiltration of the bladder, and arthritis also developed.

The localizing power of the culture from the urine was tested by intravenous injection into rabbits on seven occasions over a period of one and a half years. Twenty-four rabbits were injected, two died, and the others were chloroformed in from two to eight days. Lesions of the kidneys, chiefly of the medulla, were found in thirteen of the animals, of the kidneys and bladder in one, and of the urinary bladder, without lesions in the kidneys, in two. Lesions of the urinary tract developed in sixteen rabbits (66 per cent). Other tissues were free from lesions, with the exception of a few hemorrhages in the muscles of two of the rabbits.

Of the total of thirty rabbits injected with cultures from teeth, tonsillar tag and urine, twenty-three (77 per cent) developed lesions in the urinary tract, twenty-one developed lesions of the kidney, six of which also had lesions in the urinary bladder, and two developed lesions of the bladder only.

Intravenous injection of seventeen rabbits with the streptococcus obtained from the teeth of the dogs used in this case produced mild lesions of the medulla of the kidneys in twelve, two of these rabbits also had slight hemorrhages in the bladder, and turbidity of joint fluid, one rabbit had hemorrhages of the bladder without lesions of the kidney, and two rabbits were free from lesions. All the animals survived and were anesthetized in from two to four days after injection.

Four series of experiments were performed on dogs in this case. Three series of dogs were inoculated with cultures isolated from the urine, and one series was inoculated with cultures from an infected tooth.

In the first series the teeth of two dogs were devitalized and infected directly with the primary culture from the urine. Both dogs developed calculi. One dog died of distemper forty-six days later. The kidneys and bladder contained a large number of small, hard calculi, the stones in the kidney were often loosely adherent to the mucous membrane of the calices. The left kidney of the second dog was removed on the fifty-first day. It contained grayish-white linear streaks and small con-

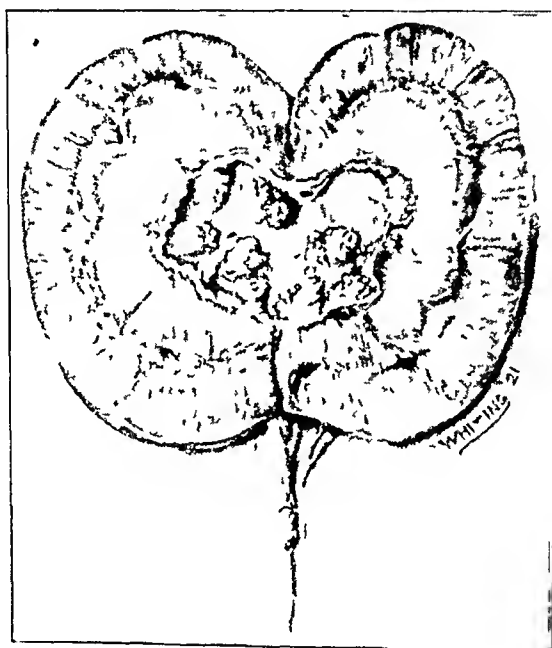


Fig 2—Kidney of a dog showing stones in the pelvis, an impacted stone in the ureter, dilatation of the pelvis, and “ascending” nephritis ( $\times 1$ )

cretions in the medulla. The operation wound healed without suppuration but the animal lost in weight, despite the fact that it ate normally. Later it became inactive, and lost much of its hair. It died seemingly of inanition on the seventy-ninth day. The right kidney was congested, contained large and small, white almost necrotic areas, often wedge-shaped in the medulla and of irregular shape in the cortex. The capsule stripped readily. The cortex was swollen, the cortical markings were distinct. The pelvis was distended with whitish mucopurulent material in which large, yellowish, angular, rough calculi were embedded (Fig 2). The shape of some conformed to the calices in which they were found. The mucous membrane of the pelvis was necrotic and hemorrhagic. The pus contained numerous hard particles

resembling sand In the right ureter there was an impacted rough stone, 3 cm from the pelvis One small stone was found in the opposite ureter 2 cm from the severed end

The bladder contained cloudy urine, with much pus, in which many small calculi were found The mucous membrane contained several hemorrhagic areas with superficial erosions Aside from cloudy swelling, no lesions of other viscera were found

The devitalized teeth were markedly discolored, but firm, the cement was in proper place, there was no swelling opposite the roots, turbid fluid was found in the pulp chambers of all four cuspids The two upper cuspids became infected secondarily Smears showed gram-negative bacilli, gram-positive diplococci, sometimes in short chains, and staphylococci in varying proportions Cultures from the infected teeth, from the liver, the substance of the kidney, the blood, the calculi and the pus in the pelvis of the right kidney yielded the streptococcus inoculated, and gram-negative bacilli and staphylococci

Sections of the right kidney showed marked necrosis of the pelvic mucous membrane, marked infiltration, chiefly by leukocytes, in the medulla immediately surrounding the pelvis, and radiating areas of similar infiltration, in some instances extending along the interlobular tubules well into the cortex On the basis of these striking results a second series of experiments, in which controls were included, was performed

The teeth of four dogs were infected with the primary culture in glucose-brain broth from the urine of the patient, and the teeth of four others, with a suspension of a mixture of arthritis strains of streptococci Four additional dogs were placed under the same conditions without devitalizing or infecting the teeth One of the four dogs whose teeth were infected with the primary culture from the urine of the patient died of distemper eleven days later Necropsy revealed extensive bronchopneumonia, cloudy swelling of the viscera, several circumscribed hemorrhages in the mucous membrane of the bladder, and streptococci and staphylococci in the urine, but no focal lesions of the kidneys There was no evidence of stone formation in the kidneys, nor of periapical infection of the teeth One dog died of distemper sixteen days after devitalization and infection of the teeth In this instance necropsy disclosed mucopurulent exudate in the bronchi extensive bronchopneumonia, coarse, usually adherent, calcareous particles resembling sand in the calices of both kidneys, but no focal lesions, cloudy swelling of the viscera, and slight evidence of periapical infection around the devitalized teeth The findings in the other two dogs were as follows

*Pathologic Findings*—June 23, 1921, the pulps were removed from the four cuspids of Dog 17 and the canals infected with the culture

from urine obtained from the patient the day previously. The urine and the roentgen-ray examinations of the dog were negative. September 5, the animal appeared to be well. The teeth and cement fillings were firm. A catheterized specimen of the urine contained a small amount of albumin, many leukocytes and calcium oxalate crystals. September 24, the left kidney was removed. Several small, yellow



Fig 3—Roentgenogram showing three stones in the right kidney of Dog 17

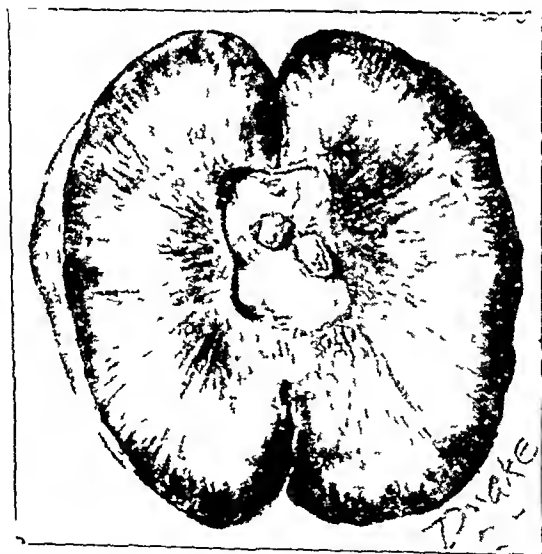


Fig 4—Kidney of Dog 17 showing stones in the pelvis, and small calcareous deposits in the medulla ( $\times 1$ )

granules, free and adherent, resembling sand, were found in the calices. The medulla and cortex were free from gross changes, but microscopically numerous small areas of round cell infiltration were found in the cortex, and in the medulla one large area of focal necrosis with marked connective tissue formation in the center, surrounded by round-cell infiltration and several small linear streaks of lime deposit, with

little surrounding infiltration. A few diplococci were found in the areas of cellular infiltration. The wound healed without suppuration, but the dog soon began to lose weight and much hair, and died October 20.

A roentgenogram made the day of its death contained three distinct shadows of stones in the right kidney (Fig. 3). The kidney appeared to be normal on the surface. The capsule stripped readily. The cortex, aside from cloudy swelling, was normal. The medulla was hyperemic, and in it were numerous small calcareous deposits in the form of small yellowish-white linear streaks and dots, which became larger in the region of the pelvis (Fig. 4). In the pelvis were three hard, yellowish, rough stones, varying in size from 2 by 3 mm to 3 by 6 mm. The mucous membrane of the pelvis was hyperemic, but otherwise appeared to be normal. The right ureter contained a small, hard, readily dislodged stone, 2 cm from the kidney. The left ureter



Fig. 5—Roentgenogram of upper jaw of Dog 17. Note the sharply circumscribed area of rarefaction over the cuspid.

was normal, as was also the mucous membrane of the bladder. In the bladder were numerous small, loose calculi, varying in size from grains of sand to 2 mm in diameter.

The urine was acid in reaction, and turbid, and the sediment contained a large number of desquamated epithelial cells, a few leukocytes and erythrocytes, and a trace of albumin. In staining smears of the sediment, a moderate number of gram-positive diplococci and an occasional coccus resembling a staphylococcus, but no bacilli, were found. There were no lesions in the other viscera.

The devitalized teeth were markedly discolored, but firm, and the cement was in the proper place. There was rarefaction of the bone opposite each of the devitalized teeth. Over the left upper incisor was a sharply circumscribed area of firm connective tissue capping the root apex (Fig. 5). The rarefied area around the root of the right upper cuspid was large, and capsulation had not occurred, it was filled with

a soft, moist and edematous, partially organizing material. The pulp chambers of all the devitalized teeth contained chocolate colored fluid, in which large numbers of gram-positive diplococci, many in short chains, and small gram-negative bacilli were found.

Shake cultures in blood-agar of the material from the rarefied area around the right upper cuspid contained large numbers of hemolytic



Fig 6—Short chain of streptococcus adjacent to an area of crystallization in a collecting tubule in the medulla of the kidney of Dog 17 Gram ( $\times 1,000$ )

colonies of gram-negative bacilli and green-producing streptococci, and colonies of staphylococci. Blood-agar plate cultures from the medulla of the kidney from one washed and crushed stone, and from the sediment of the urine, did not yield growth, whereas glucose-brain broth cultures of the kidney yielded a pure culture of the diplostreptococcus,

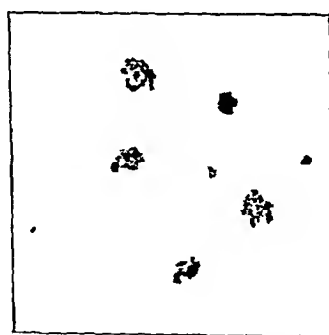


Fig 7—Rough, angular calculi from the pelvis of the left kidney of Dog 18 ( $\times 3$ )

and of the stone, streptococci and staphylococci. Cultures from the canal of the left lower cuspid yielded the streptococcus and staphylococcus.

Microscopic examination of sections of the right kidney revealed numerous sharply circumscribed areas in the medulla in which crystallization and precipitation of salts were found. These areas varied

greatly in size, some containing only a few well defined crystals, while others were made up of large aggregations of crystalline and amorphous material. In all of the latter, cellular infiltration was slight, and in some, particularly in the areas showing only a few crystals, it was possible to demonstrate diplococci, and at times streptococci in the tissues immediately adjacent to the areas of crystallization (Fig 6)

June 23, 1921, the four cusps in Dog 18 were devitalized and the pulp chambers infected with dense suspension of the primary culture of the urine. Blood-agar plates of the suspension inoculated yielded almost pure growth of green-producing streptococcus and a few staphylococcus colonies. Before the inoculation the urine was normal and roentgenograms of the kidney region were negative.

September 24, the dog appeared to be well, and the left kidney was

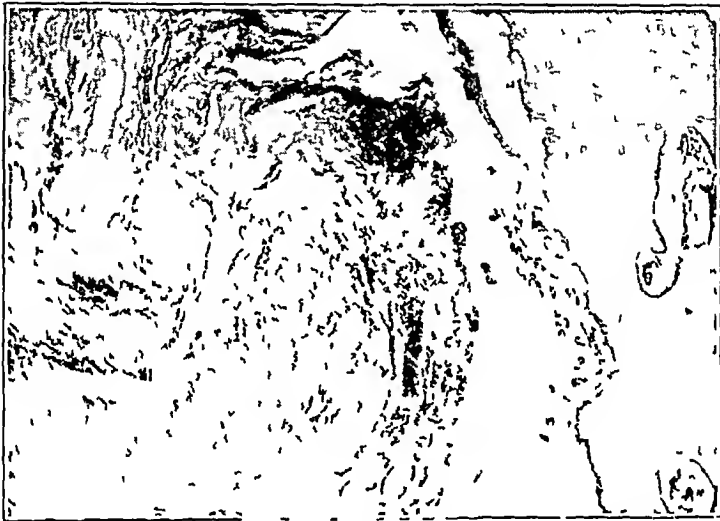


Fig 8—Granuloma over the apex of right upper cuspid of Dog 18. Note the irregular cellular infiltration and the invasion of the bony structure. Hematoxylin and eosin ( $\times 70$ )

removed. Many small, loosely adherent, irregular calcareous particles were found in the calices (Fig 7). Cultures from this kidney were negative. Microscopic examination of sections revealed one rather large area of focal necrosis, with marked leukocytic and round-cell infiltration low in the medulla, and a few smaller areas of interstitial infiltration. A few diplococci were found in the area of focal necrosis.

Recovery following the operation was prompt, and the wound healed without suppuration. The animal appeared well October 4, but a catheterized specimen of urine contained albumin, a few leukocytes and many calcium oxalate crystals. October 25, emaciation was marked. The animal was chloroformed.

A roentgenogram of the kidney revealed two small, round shadows. The capsule stripped readily. In splitting open the kidney a grating



of the knife edge was noted. The cortex was normal. The medulla contained whitish linear streaks near the pelvis, some of these were calcareous, and in one, projecting into the pelvis, a calculus measuring 3 mm in diameter was found. In the pelvis were two rather large stones, and in the calices, six smaller ragged ones, the larger stones were free, the smaller ones adherent to the mucous membrane. The ureters and bladder were free from stones and lesions. No lesions were found in the other viscera.

The left lower cuspid had sloughed away, the alveolar socket was filled with pus, and a subcutaneous fistula had formed. Rarefaction was found in the periapical region of the remaining cuspids, and the areas were filled with dense connective tissue (Fig 8). Sections of

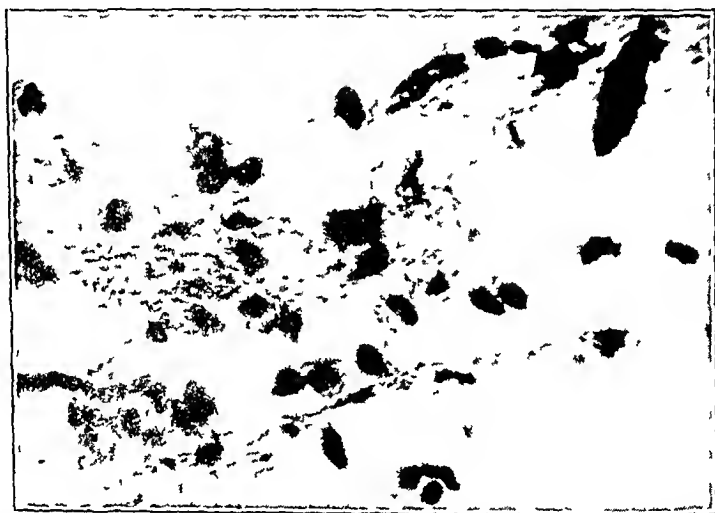


Fig 9—Diplococci adjacent to bone in granuloma shown in Figure 8. Gram-Weigert ( $\times 1,000$ )

one of these areas revealed marked leukocytic infiltration, varying greatly in intensity, and invasion and absorption of the bony structure. Diplococci and streptococci were found in the areas of cellular infiltration, especially where the bone was eroded (Fig 9). The pulp chambers were of moderate size and contained thick, chocolate colored pus, in which large numbers of gram-positive diplococci, often in short chains, were found. Cultures from the pus in two of the teeth, and from one of three washed and crushed stones, yielded pure growths of the streptococcus. These cultures were injected intravenously into three rabbits each. All the animals were well at the end of forty-eight hours, when they were anesthetized. Two in each group had mild lesions in the medulla of the kidney, and one in each had lesions of the bladder. Two also had a few lesions in the muscles, but no lesions were found elsewhere. The fermentative power of the strepto-

coccus from the right upper cuspid was identical to that of the streptococcus from the kidney of Dog 17 and from the urine of the patient. Glucose, maltose, saccharose and raffinose were fermented, while mannite, salicin and inulin were not. The streptococcus from the stone fermented glucose, maltose and salicin, but not saccharose, raffinose, mannite or inulin.

Sections of the right kidney revealed a number of small sharply circumscribed areas of interstitial infiltration with leukocytes and round cells, and areas of varying size containing crystals resembling calcium oxalate in which leukocytic and round-cell infiltration were absent or slight. These were largest in the papillae just beneath the mucous membrane of the pelvis (Fig 10), became progressively smaller up



Fig 10—Area of crystallization, and slight infiltration in medulla adjacent to the pelvis in the right kidney of Dog 18. Hematoxylin and eosin (+220)

along the tubules in the medulla, and were absent in the cortex. The demonstration of organisms in the larger areas was not accomplished, while adjacent to the smaller areas, especially those that still contained a few infiltrating cells and homogeneous exudate, gram-staining diplococci, sometimes in short chains, were found (Fig 11).

The mixture of streptococci from arthritis inoculated into the teeth of four of the control dogs represented four strains isolated from four cases of subacute arthritis. They were cultivated from the joints of rabbits that developed arthritis following intravenous injection of the primary culture in glucose-brain broth from infected teeth or tonsils. Each strain had been kept in dense suspension in glycerin and concentrated salt solution for from one month to six weeks. Plating on blood-agar of the suspension inoculated yielded a large number of colonies of green-producing streptococci.

One of these dogs died on the sixty-second day, after marked loss in weight. No gross lesions of the joints, muscles, or kidneys were found. One died of distemper five days after devitalization and infection of the teeth, and one in fourteen days. No stones were found, nor was any arthritis noted. One dog gained in weight. The left kidney was removed ninety-nine days after the teeth were infected, and the animal was chloroformed on the one hundred and twentieth day. Both kidneys and the joints were normal.

A medium sized granuloma was found capping each of the four devitalized teeth. The pulp chambers of three contained small amounts of chocolate colored pus. From these the green-producing streptococci, a few staphylococci, and gram-negative bacilli were isolated. In the



Fig. 11—Diplococci and leukocytes adjacent to an area (lower portion of field) showing crystallization in the medulla. Gram-Weigert ( $\times 1,000$ )

other tooth the pulp chamber was dry, and cultures yielded the streptococcus in pure growth. This was injected intravenously into two rabbits of the same weight. Both animals were disinclined to hop, and were anesthetized forty-eight hours after injection. One rabbit had suppurative arthritis of both knee joints and one shoulder joint, in the other rabbit there was slighter turbidity of the knee joint fluid, and marked hemorrhages and edema of the muscles around the knee joints near the tendinous ends.

A pure culture of the streptococcus was isolated from the blood and joints of each rabbit. Four additional rabbits were injected, two each with the cultures from the blood of these rabbits, one representing a pure arthritis strain, the other a myositis-arthritis strain. All four rabbits survived, sat quietly, and were disinclined to hop. They were anesthetized forty-eight hours after injection. The two injected with

the pure arthritis strain developed suppurative arthritis of both knee joints shoulder and ankle joints, one without lesions of muscles, the other with only a few small hemorrhages in the tendinous end of the muscles on the inner side of the left knee joint. The two injected with the myositis-arthritis strain developed marked periarticular hemorrhages of ligaments and adjacent muscles, and relatively slight turbidity of the joint fluids, the picture of a periartthritis. Cultures from joint fluids in all again yielded the streptococcus in pure form. No lesions were found in the kidneys of the six rabbits injected.

Of the four additional control dogs, one died of distemper fourteen days after being placed under conditions similar to those of the dogs whose teeth were devitalized and infected. The left kidney of each of the other three dogs was removed after ninety-nine, ninety-nine, and 140 days, and the dogs were killed after 120, 120, and 118 days, respectively. The kidney and urinary bladder in all of these were free from stones and were otherwise normal. Cultures in glucose-brain broth from the apical ends and pulps of two vital teeth, and from the kidney structure of two of the dogs proved negative. Sections of the right kidney of each of the three dogs were examined and all were free from lesions. The urine remained normal, roentgenograms remained negative, and the animals gained in weight and were active and playful throughout the experiment.

In the third series of experiments, begun March 8, 1922, there were four dogs whose teeth were infected with the primary culture of the streptococcus from the urine of this patient during a quiescent interval, two dogs whose teeth were merely devitalized, and four dogs whose teeth were devitalized and infected with an avirulent strain of *Staphylococcus albus*. All of the ten dogs remained well and were anesthetized in from three to five months. Three of the dogs in the first group revealed small calculi in the medulla and calices at necropsy, and microscopic deposits of lime salts and areas of cellular infiltration in the medulla. The fourth dog in this group, and the six control dogs were free from calculi and other lesions. The streptococcus isolated from the medulla of the kidneys of the three dogs that had lesions was injected intravenously into ten rabbits. Seven developed lesions in the medulla of the kidneys, three were free from lesions.

The fourth series of experiments was conducted on two dogs whose teeth were inoculated with the streptococcus from the tooth extracted October 21, 1921, and on two control dogs inoculated with the streptococcus from the tonsils of a patient with vague urinary symptoms. The first two dogs developed gross and microscopic calculi in the medulla or calices of the kidneys, and areas of active infiltration in the medulla. The control dogs were free from calculi and other lesions.

## RESULTS IN THE NINE CASES STUDIED

Owing to the numerous instances of beneficial effects in other diseases from the removal of foci of infection and to the results obtained in our first case, the tonsils were removed and infected teeth extracted in the other patients studied. The extracted teeth and extirpated tonsils afforded us opportunity to obtain proper cultures for experimental studies.

All of the patients studied were men. Their ages ranged from 33 to 60 years. All were suffering from nephrolithiasis, had had typical renal attacks of from three to twenty years' duration, and the interval from the last attack to the time of our study ranged from two weeks to nine months. A history of acute infection which appeared to be a factor in the genesis of the urinary symptoms was obtained from three of the patients. Cultures were made from the urine of five of the patients. From three of these urines streptococci, usually with staphylococci and *Bacillus coli*, were isolated. Foci of infection were found in the teeth or tonsils of all. The number of pulpless teeth showing periapical infection varied from one to seven in each patient. Most of the infected teeth had been rendered pulpless many years prior to our study. The teeth of dogs were infected with cultures from teeth, tonsils, and urine of one patient, from teeth and tonsils of two, from infected teeth only of four, and from tonsils only of two.

Twenty of the thirty-four dogs used in the experiments developed calculi and other lesions in the urinary tract, readily visible at necropsy. Twenty-six (75 per cent) revealed microscopic calculi in the medulla of the kidney, and twenty had localized areas of active cellular infiltration in the medulla. Thirty dogs (87 per cent) revealed either calculi or localized lesions in the medulla, or both. Streptococci or diplococci were demonstrated in, or adjacent to, lesions in the kidney in sixteen dogs, all of which showed active focal lesions on microscopic examination. Positive results were obtained in eight of the nine cases. In the negative case the teeth of only one dog were infected.

The duration of the experiments yielding positive results was one month in two of the dogs, from two to three months in eight, from three to six months in twelve, from seven to eight months in six, and ten months in two. The duration of the four negative experiments was only eleven, fifteen, thirty and forty-five days, respectively, because of death from distemper.

The number of dogs whose teeth were infected with cultures from the patients varied from one to twelve in each case. In two cases only one dog was used; in three cases two dogs; in two cases, four dogs; in one case six dogs; and in one case twelve dogs were used. The teeth of eighteen dogs were inoculated with cultures obtained from infected teeth; six with cultures from tonsils; and ten with cultures

from the urine. Twenty of the dogs were anesthetized and fourteen died of intercurrent infection or as the result of the induced focal infection.

In nearly all instances cultures from the pus found in the pulp chambers which showed many streptococci and leukocytes in smears, yielded streptococci resembling those inoculated, usually with small gram-negative bacilli. This was true alike of the three cuspids infected at the time of the operation and the one cuspid in each dog which was merely devitalized and sealed in a sterile manner.

The localizing power in rabbits of the streptococcus from the teeth was tested at the end of each experiment in sixteen of the thirty-four dogs.

Forty-two rabbits were injected. Focal lesions were found in the medulla of the kidneys in twenty-one. Lesions in other organs were rarely obtained. Five had lesions in the periosteum opposite the roots of the incisors, three in skeletal muscles, three in the myocardium, two in joints, one in the gallbladder, and one had ulcer of the stomach.

Of the sixteen dogs from whose teeth cultures were made and injected intravenously into rabbits, ten, representing four cases, showed microscopic evidence of active focal lesions in the medulla of the kidney. Of the twenty-eight rabbits injected, twenty-one developed focal lesions in the medulla and seven showed no changes. The remaining six dogs, representing four cases, showed no microscopic evidence of active lesions in the kidney, and all of the fourteen rabbits injected remained free from lesions in the kidneys.

Streptococci resembling those inoculated into the teeth were isolated from the urine at necropsy in fifteen of the twenty-three dogs in which cultures were made from the kidney in seven of twenty-seven dogs, and from renal calculi in three of six dogs. The positive cultures from the urinary tract were all obtained from dogs whose kidneys showed active lesions on microscopic examination. The primary cultures of the streptococcus from the urine, kidney, or calculi of five dogs, representing three cases, were injected intravenously into sixteen rabbits. Of these eleven revealed localized lesions in the medulla of the kidneys, while five remained free from lesions.

The staphylococcus which was isolated in small numbers from the urine of our first patient, and from several stones and some of the teeth of the dogs always failed to localize in the kidney on intravenous injection into rabbits and was not demonstrable in the areas showing beginning stone formation.

The strains of streptococci from the different cases with which positive results were obtained were much alike. All produced small, rather dry, nonadherent green colonies on blood-agar plates, all were of a low grade of virulency, and produced marked acidity in glucose broth.

The lesions in the kidneys of rabbits following intravenous injection were similar to the active lesions in the dogs. They were not numerous, and not necrotic, and were nearly always small and limited to the medulla. Those following the injection of the urine cultures were the more pronounced. By placing thin pieces of fresh tissues immediately into solutions of neutral red, and by treating sections of the fixed tissues with nitrate of silver, it was found that deposition of lime salts occurred in lesions in the kidney, and in a few instances in lesions of the myocardium, as early as forty-eight hours after injection. Microscopic examination of the kidneys of the dogs showed three main types of lesions, sharply circumscribed areas of leukocytic infiltration between the collecting tubules, more diffuse areas of round-cell infiltration (Fig 12), and deposits of oxalate crystals (Fig 10)



Fig 12—Section of the medulla of the kidney of a dog whose teeth were devitalized and infected five months previously. Note the four areas of calcium deposit and the linear areas of cellular infiltration. Hematoxylin and eosin ( $\times 50$ )

or amorphous lime salts, with little or no surrounding cellular infiltration (Fig 12). The number of bacteria in the lesions was always small (Figs 6, 11, 13, and 15), long search was often necessary for their demonstration. They were never found in normal tissue remote from lesions nor in the kidneys of ten dogs in which localized areas of cellular infiltration were absent and in which the areas of lime deposits had healed. Sections of other viscera in some of the dogs that had stones were uniformly free from changes.

#### CONTROL EXPERIMENTS

Besides the twelve control dogs in our first case, we have studied the results in twenty-three additional dogs whose teeth were infected

with cultures of streptococci or staphylococci from sources other than nephrolithiasis, and which were kept under the same conditions with regard to diet, and so forth, as those inoculated with the nephrolithiasis strains. Areas of rarefaction around the apices of the infected teeth from which the inoculated organisms were recovered were found in most instances. Five (14 per cent) of the thirty-five animals revealed calculi and lesions of the medulla of the kidneys. The calculi were small and situated chiefly in the medulla or calices. Sections revealed small localized areas of infiltration and areas of lime deposits in the medulla, with little or no cellular infiltration, in which diplococci were demonstrated. Since the organisms inoculated into the teeth of these dogs had no affinity for the kidney, it was thought that the small calculi found in this series were of spontaneous origin, and that calculi

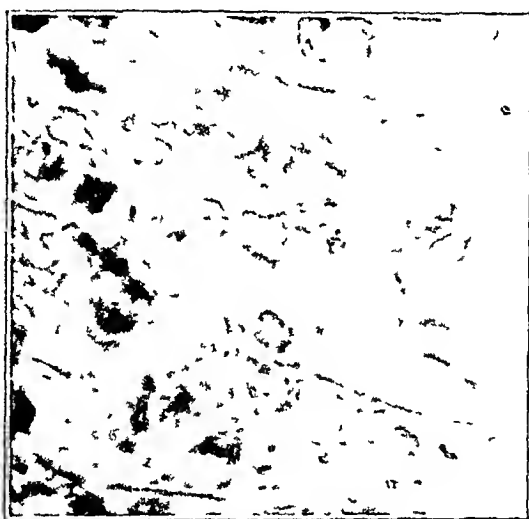


Fig. 13—Diplococci in the area of cellular infiltration shown in Figure 12 Gram ( $\times 1,000$ )

in dogs may also be due to infection. Through the kindness of Dr. Haidenburgh we have had opportunity to test this hypothesis experimentally and are able to include, as a further check on our experiments, the results of his routine examination of dogs kept under similar conditions during the course of our study. Of 433 dogs examined, fifty (11 per cent) had urinary calculi. In most of these the calculi were small, flat and loosely adherent to the mucous membrane of the calices. None was as large as those illustrated in Figures 2 and 4. The gums around the teeth of many showed varying degrees of infection. Urinary calculi were not found at necropsies performed by one of us on 581 dogs over a period of ten years. According to Hutyrá and Marek,<sup>4</sup>

<sup>4</sup> Hutyrá, F., and Marek, J. *Special Pathology and Therapeutics of the Diseases of Domestic Animals*, London, Baillière, Tindall and Cox, 1 1149, 1912



calculi were found in only twelve (0.38 per cent) of 3,301 dogs examined at the Dresden Pathological Institute. The experience of others indicates a general low incidence of this condition in normal dogs.

The experiments to determine the etiology of spontaneous calculi in dogs consisted of culturing the medulla of the kidneys containing calculi, and the washed and crushed stones, of testing the localizing power of freshly isolated cultures on intravenous injection in rabbits, and of inoculating the teeth of dogs with the organisms isolated from the induced lesions in the kidneys of rabbits. Pure cultures of streptococci were isolated from the medulla of the kidney or from the stones of each of five dogs showing spontaneous calculi. One of these produced hemolytic colonies on blood-agar plates, one indifferent colonies, and three green colonies. The indifferent strain was injected into

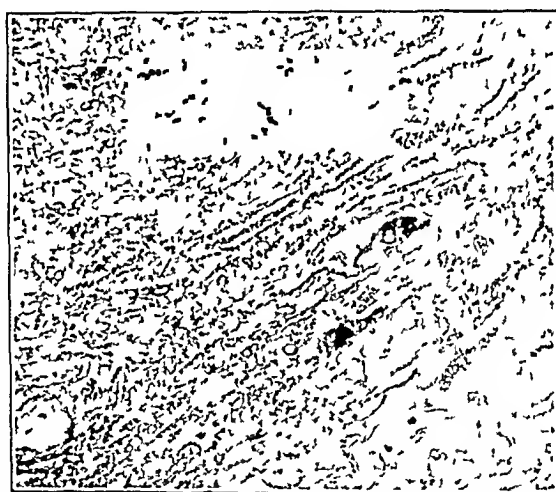


Fig. 14.—Section of the papilla of a dog that developed spontaneous calculi. Note the areas of lime deposit, and slight cellular infiltration. Hematoxylin and eosin ( $\times 50$ ).

four rabbits, and one of the green-producing strains into one rabbit. All remained well and free from lesions, and the strains were lost. One of the remaining green-producing strains produced lesions of the medulla of the kidneys in two rabbits injected. The primary culture of the third green-producing strain isolated from the stone of one of these dogs produced lesions in the medulla in three of four rabbits and one of two dogs injected intravenously. The strain from one of the positive rabbits produced lesions in the medulla of the kidneys of two rabbits, and the strain from the positive dog, in the one rabbit injected. Cultures from the kidneys showing lesions were positive in every instance and negative where no lesions were found. Cultures from the blood were negative in all. The strain isolated from the kidney of this dog culturally and morphologically identical to the one isolated from the stones, was without effect in four rabbits

injected. No lesions were found, and cultures from the kidneys and blood were sterile.

The hemolytic streptococcus in the third subculture was injected intravenously into two rabbits. Both developed lesions in the medulla of the kidneys, and cultures of the urine and kidneys yielded pure growths of the streptococcus injected. This strain produced lesions in all of three rabbits injected. The culture from the kidney of one of these was then injected into two rabbits. Both died, and marked lesions of the kidneys were found at necropsy. The culture from the kidney of one of these in turn was inoculated into the teeth of two dogs. They lost weight but seemed well six months later, when they were anesthetized. Both had developed calculi in each kidney, demonstrable by the roentgen ray. Sections revealed localized areas of lime deposits and circumscribed areas of relatively slight round-cell infiltra-

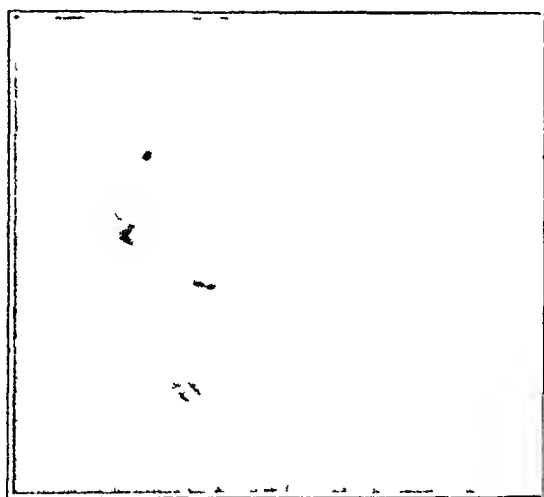


Fig. 15—Chain of two diplococci immediately adjacent to the largest area of calcium deposit shown in Figure 14. Gram ( $\times 1,000$ )

tion in the medulla (Fig. 14), in which diplococci were demonstrable (Fig. 15). The streptococcus inoculated into the teeth was isolated from the teeth and from the kidney stones and urine in pure culture at the end of the experiments. The cultures from the stones and kidneys produced lesions in the medulla of the kidney in all of seven rabbits injected intravenously, from which the streptococcus was isolated in pure culture in every instance. The blood was sterile in six and contained the organism in one.

Four control dogs placed under identical conditions during the course of the experiment were found free from calculi.

#### SUMMARY AND DISCUSSION

The streptococcus inoculated into the pulp canals was isolated from the infected material in the root canals or the periapical tissues of the pulpless teeth at the end of each experiment. This was true alike of

the three cuspids which were devitalized and infected at the beginning of the experiment and of the cuspid which was devitalized but not infected. In some instances secondary infection by a small gram-negative bacillus, and more rarely by a staphylococcus, had occurred. The streptococci in the teeth in which secondary infection had not occurred were especially numerous at the periphery of well formed granulomas and where the bone was being absorbed. The findings around the teeth were similar to those following the devitalization of teeth in persons, as practiced in dentistry: the infected teeth became discolored, but remained firmly in place in the alveolar sockets, the infection caused rarefaction and absorption of bone in the periapical region without swelling, pain, or tenderness, and the cellular infiltration and distribution of the bacteria of well formed granulomas were also similar.<sup>5</sup> The experimentally produced chronic foci, aside from being the source of the streptococcus which tended to localize electively in the urinary tract, appeared to have a general deleterious effect. Some of the dogs lost markedly in weight and became more susceptible to intercurrent infection. This was particularly true in those in which unusually large areas of infection around the teeth had developed and in which the renal calculi were large. This finding supports the interpretation by Osborne and Mendel<sup>6</sup> of the infectious origin of urinary calculi observed in rats (eighty-one of 857) fed on a diet deficient in fat soluble vitamins.

It is not clear why the four dogs infected with the arthritis streptococci failed to develop arthritis. Active infection around the teeth was found in all. The streptococcus from the pulp chamber in one of the dogs inoculated four months previously had retained its affinity for the joints of rabbits on intravenous injection. It would seem, therefore, that the joints of these dogs were not affected because of high resistance of these structures to invasion by this organism during the relatively short duration of the experiment.

Calculi or lesions of the medulla were produced in 87 per cent of the dogs whose teeth were infected with streptococci from the urine, infected teeth, and tonsils of nine patients with typical nephrolithiasis. The duration of the experiment on the dogs in which the findings were negative was too short for stones to form. This is in sharp contrast to the findings in an equal number of dogs whose teeth were infected with strains from other sources, and to those of a larger series kept under the same conditions but in which the teeth were not infected.

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The experimentally produced calculi were similar in physical properties and chemical composition to those found in nephrolithiasis in man. The number and size of the stones were often proportional to the duration of the experiment. The other findings in the urinary tract were also similar to those occurring in patients with this disease.

If albumin, pus and blood were present in the urine, there were only small amounts, and the lesions in the medulla of the kidneys were relatively slight unless ureteral obstruction from an impacted calculus occurred when marked ascending infection developed just as it commonly does in patients with partial obstruction of the ureter, and as produced experimentally in dogs by Keith and Snowden.<sup>7</sup>

The streptococcus inoculated into the teeth of dogs was isolated from the kidneys, from some of the stones and from the teeth at the end of the experiments, and its elective affinity for the urinary tract in rabbits was demonstrated on intravenous injection. The streptococcus from the teeth of dogs that showed active lesions in the kidneys had retained specific affinity for the kidneys of rabbits, while those from the dogs that showed no lesions or only healed lesions had lost this peculiar localizing power. The organism was found in the lesions in the substance of the kidney where crystallization and stone formation were beginning.

The results of our experiments and the clinical study by Keyser and Braasch,<sup>8</sup> and others<sup>9</sup> indicate that the factor of focal and other infections should be given thorough consideration in the management of cases of nephrolithiasis. And may not a stone-forming infection account in part for the unusual prevalence of this condition in certain localities? The demonstration of the presence of the microorganisms precisely where precipitation and crystallization begin suggests strongly that the mechanism of the production of stone is largely a local process and that the reactions incited produce the physicochemical conditions necessary, such as the nucleus and organic framework, for the formation of calculi. The common occurrence, however, of unusually large numbers of calcium oxalate and other crystals in the urine and in the medulla of the kidneys of the dogs that developed calculi, and the loss in weight, suggest that more general effects of infection may also play a part.

The conclusion that primary urinary calculi are often due to streptococci which have elective affinity for the urinary tract and, it would seem, specific power to incite the conditions necessary for their formation seems justified.

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# A STUDY OF MACROPHAGES IN THE HUMAN BLOOD WITH SPECIAL REFERENCE TO THEIR PRESENCE IN TWO CASES OF SUBACUTE BACTERIAL ENDOCARDITIS \*

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It is the purpose of this paper to present two cases of malignant endocarditis associated with *Streptococcus viridans* septicemia, showing some unusual cells termed macrophages in the peripheral blood. The morphologic and functional characteristics of these cells corresponded closely with cells produced experimentally in rabbits by one of us.<sup>1</sup> It is because of this similarity that we hope to offer some suggestions which may help to clarify the nature and relationship of these and other mononuclear cells found in the blood.

The cells which we term macrophages (Metchinkoff, H. M. Evans) because one of their striking characteristics is a marked power of phagocytosis, have been synonymously termed pyrhol cells (Goldman), adventitia cells (Marchand), histogenous macrophages (F. A. Evans), histiocytes (Aschoff, Kiyono), resting wandering or polyblast cells (Maksimow), rhagiocrine cells (Renaut), endothelial leukocytes (Malloy), and clasmatocytes (Ranvier), although some of the above terms included in their scope additional mononuclear cells to those described herein.

A wide range of pathologic conditions seem to stimulate the production and release of these cells into the peripheral blood, although they have never been found there in normal humans or other mammals. Thus mononuclear phagocytic cells have been described in active endocarditis by Schilling,<sup>2</sup> Leede,<sup>3</sup> Hynek,<sup>4</sup> and Netousek<sup>5</sup> (the latter also observing them in experimental septicemias), in typhoid fever by

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\* From the Departments of Medicine and Anatomy of the University of California Medical School.

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Eichorst,<sup>6</sup> Mallory,<sup>7</sup> McCallum,<sup>8</sup> and Netausek<sup>5</sup> (in typhoid vaccination by Miller and Pepper<sup>9</sup>), in malaria by Pappenheim,<sup>10</sup> Schilling<sup>2</sup> and Bushnell,<sup>11</sup> in tuberculosis with mild nephritis, and mesenteric tuberculosis with secondary sepsis by Schilling,<sup>2</sup> in cholera by Netausek,<sup>12</sup> in a chronic heart case with intestinal parasites and erysipelas by Van Nuys<sup>13</sup> and in a chronic heart case in which they were found in localized leukocytosis in the lobes of both ears only, by Bartlett<sup>14</sup>. They were first experimentally produced by Aschoff and Kiyono<sup>15</sup>.

In these cases there is apparently a definite etiologic agent. There may be pointed out in addition a series of cases with obscure cause, in which at least recognized irritating or stimulating material such as toxins, colloids or particulate matter is not known to be thrown into the blood stream. Such are the cases of monocyte (transitional) leukemias (Schilling, Reschad and Schilling,<sup>16</sup> Jochman and Bluhdorn<sup>17</sup> of Van Jaksch's chlorosis anemia and anemia with splenomegaly (former two cases of Netausek, latter of Fr Krauss<sup>18</sup>), of "fatal anemia" (Rowley<sup>19</sup>), and possibly of paroxysmal hemoglobinuria (Ehrlich, Eason, Kommer and Meyer<sup>20</sup>), and of the blood distally to the point at which the chief vein of a limb has been ligated proximally.

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18 Krauss, Fr. Ein Fall von Splenomegalie, *Berl klin Wchnschr* **50** 1421-1423, 1913.

19 Rowley, Mary W. A Fatal Anemia with Enormous Numbers of Circulating Phagocytes, *J Exper M* **10** 78-97, 1908.

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TABLE 1—THE BLOOD FINDINGS IN THE CASE OF C P

Date, 1921	Total White Count 4,800	Poly morpho nuclear neutrophils per Cent	Myelo cytes, per Cent	Fosho phils, per Cent	Baso phils per Cent	Lympho cytes per Cent	Macro phages per Cent	Intermedi ate Forms, per Cent	Mono cytes, per Cent	Plate lets	Erythro cytes in Millions	Remarks
5/ 5			1				+				3.27	Blood culture, streptococcus viridans in 5 days sputum culture, streptococcus viridans
5/22							0					
6/ 4	13,200						1				3.52	
6/ 5								30	5			
6/ 6							0	2	17			
6/ 7							0		9			
6/ 9		66.5	0	0	0	30.5	0	0	4			
6/10							0	1	4			
6/11, 10:30 a m								9	5			Blood culture, streptococcus viridans after 5 days
2:30 p m	11,000									++		One hour before transfusion, 15 hours after transfusion
6/12, 2:30 p m								1?	3			Identical result with fixed and vitally stained films
6/14		44	0	1	0.5	16.5	16 complete gradation 29 complete gradation 39 complete gradation					Twenty four hours after transfusion
6/16										+		Bleeding time 4 minutes
6/17										++		
		74.5	0	0.5	0	17	0	6				Fixed film from splenic puncture numerically identical with vitally stained film
							0	8				Fixed film from ear
6/19							0	1/2				Vitally stained film from ear
							0	8				

Date	Time	Radiation	Platelets	Notes
6/21	11 00 a m			
	3 40 p m			
6/22	6 40 p m			
6/23	12 m	6 000		
	4 00 p m			
	5 00 p m			
6/24				
6/25		6 000		
6/26		6 000		
		7 000		
6/29				
7/ 2				
7/ 5				
7/10				
7/12		66		
7/13		5,200		
7/16				
7/18 postmortem		9 000		
Right heart				
Left heart				



(Netousek,<sup>5</sup> and Evans and Schuleman) The two heart cases mentioned above did not come to necropsy and because of the obscurity of any active lesion, and particularly in the unique case of Bartlett's, they may be included in the latter of these two rough divisions

#### REPORT OF CASES

Two cases, C P and E W, will be presented, with the inclusion of all important clinical data except the morphologic blood findings (Tables 1, 2 and 3)

CASE 1—C P, male, age 18, stenographer, was seen on the medical service of the University of California Hospital

*Family History*—Essentially negative

*Past History*—Pneumonia at 3 months, pertussis at 18 months, measles and mumps at 5 years Bitten by rabid dog at 12 years, had Pasteur treat-



Figure 1

Fig 1—Macrophage from peripheral blood of C P, showing phagocytized material Giemsa  $\times 1500$



Figure 2

Fig 2—Macrophage from peripheral blood of C P showing long attenuated process Giemsa  $\times 1500$

ments No symptoms of rabies developed Influenza in 1918, at 16 years Apparently uncomplicated

*Present Illness*—Following the attack of pneumonia at the age of 3 months, convalescence was prolonged, and in a few weeks he became severely ill again Then a valvular heart condition was discovered by the family physician, which was considered to be due to the pneumonia Since then the patient has lived a restricted cardiac life Dyspnea, cyanosis and weakness on exertion, with frequent attacks of "bronchitis" supervened Otherwise he was well until September 1920 eight months before entry, when he had chills and fever, coming every other day for about two weeks Oct 18, 1920, seven months before entry patient collapsed, became pale and complained of pain in the left hip Thigh was flexed on abdomen, pain continued for two or three days Cyanosis of lips and finger tips was noted He was in bed five weeks but did not regain strength after rising and on December 20 patient had another chill

and was confined to bed again. Severe bronchitis was diagnosed by the family physician. No dyspnea or cyanosis was complained of during this period. He was an invalid until March, 1921, when he improved slightly and up to entry, May 5, 1921, he felt fairly well. Twelve days before entry, he had another attack of "bronchitis" and vomiting. Purpura appeared two days before entry and there has been a history of previous petechiae. Edema of feet and ankles was noted once prior to entry.

TABLE 2—BLOOD FINDINGS IN THE CASE OF E. W.

Date	Erythrocytes, Millions	Absolute leukocyte Count	Polymorpho-nuclear neutrophils per Cent	Eosinophils per Cent	Myelocytes, per Cent	Lymphocytes, per Cent	Macrophages per Cent	Intermediate Forms	Mono-cytes, per Cent	Platelets
1/24	2.4	6,800	70	1	0	19	8		2	+
1/25	3.27	8,200	51	1	0	9	3		4	
1/26		11,200								
1/27		10,200								
1/28		14,000								
1/29		11,000								
1/31		16,700								
2/4		21,000								
2/6		20,000								
2/10		12,600								
2/14		5,000								
2/15		10,000								
2/21		91,000	66	1	1	9				
2/22, 9:00 a m		51,000								
2/22, 2:00 p m		21,000								
2/27, 9:30 p m		54,000								
2/27, 10:30 a m										
2/27, 7:15 p m			0.5			4.5				
Died at 7:30 p m										

++ Moderate excess of platelets in smear

+++ Extreme excess of platelets in smear

Bracketed figures include in percentage all forms covered by bracket

TABLE 3—OBSERVATIONS ON JUNE 24, 1921, IN CASE OF C. P.

Time	Temperature	Pulse	Respiration	Per Cent Macrophages, Intermediate Types and Mono-cytes	Remarks
7:30 a m					Sponge bath
8:00 a m					Breakfast
8:30 a m	37.6	116	24	40	
10:00 a m				23.5	
11:00 a m					Luncheon
11:30 a m					
12:00 m	36.8	112	28	38	
12:30 p m				19	
2:00 p m					Lemonade
2:30 p m					Visitors 2:00-4:30 p m
3:30 p m				7.5	
4:00 p m	37.0	108	32		Stool
4:30 p m					Supper
5:00 p m				15	
6:30 p m				21	
8:00 p m	37.1	106	32		Sandwich

*Physical Examination*—On admission. Punctate purpura on extremities. Malar flush with cyanosis of lips and fingers. Signs of aortic and mitral stenosis and insufficiency, with loud systolic murmur over entire precordia predominating. Liver and spleen enlarged and tender.

May 21. Lungs negative at both bases. Murmurs persisted and a systolic thrill was noted over the precordium most marked at the apex.

Physical condition was approximately the same until June 23, when urine, which had been negative for several weeks, showed an occasional cast, red blood cell, leukocyte and a faint trace of albumin

July 2, edema of extremities and face was noted with a small amount of ascites. Pustules developed on the skin July 8. Edema and ascites increased. Fundus examination showed some blurring of disc margins. Crepitant rales were present at base of lungs.

July 17, peripheral edema decreased under Karrel diet but edema of lungs and ascites remained unchanged. Respiration and pulse increased and temperature rose from 37 to 38 C. Patient developed decubitus on both scapulae. Heart sounds were fainter. Murmurs constant throughout. Hemorrhagic spots over extremities. Patient died July 18 after short period of delirium.

*Laboratory Findings*—Blood Counts. The results of various counts are shown in Tables 1 and 3 and Charts 1 and 3.

Urine. May 5 trace of albumin. Many hyaline and granular casts. Few red blood cells and leukocytes and many epithelial cells.



Fig 3—Macrophage from peripheral blood of E. W. showing large amount of phagocytized material and vacuolization. Wright's stain.  $\times 1250$

July 23, decrease of number of casts and amount of albumin up to July 23 when shower of red blood cells occurred and increase of leukocytes was noted. Albumin increased to trace on July 6. Casts varied in showers.

Urine Culture. *Streptococcus viridans* on July 6.

Stools negative.

Blood chemistry. urea nitrogen, 35, nonprotein nitrogen, 64, creatinin, 2.52.

Blood Culture. Showed *Streptococcus viridans* on several occasions. Patient treated by injections of serum of brother who had been given repeated doses of killed cultures of *Streptococcus viridans* vaccine made from patient's organisms.

*Clinical Diagnosis*—Subacute bacterial endocarditis, involving aortic and mitral valves. *Streptococcus viridans* septicemia.

CASE 2—E. W. male, Aged 65, millwright, was observed by one of us on the West Medical Service. Drs. R. C. Cabot and R. I. Lee of the Massachusetts General Hospital. Boston. January-February, 1916.

*Family History*—Essentially negative.

*Past History*—Jaundice at 4 typhoid at 16, from five to ten years gaseous eructations when a young man Frequent sore throat up to five years ago Pleurisy at 62 History of loss of hair (transient) five or six years ago, and of brown papular rash of one week's duration one year ago Venereal diseases denied Habits Alcohol to excess for past six months Drinks from ten to twenty glasses of ale per day Weight Lost 40 pounds in past six months

*Present Illness*—Noted weakness six months before entry after alcoholic excess One week later severe diarrhea set in, persisted three weeks, stools dark brown fluid with mucus but no blood After two weeks treatment movements decreased and now he has three or four a day, semi-fluid, yellowish with some mucus and no blood Increased asthenia, lethargy and loss of weight up to present There is dyspnea without exertion, which is relieved on coughing Raises daily about 1 ounce of ropey, transparent, blood free sputum Chills in past two days No edema

*Physical Examination*—Negative, except that pupils are sluggish to light and distance Slight dullness and few coarse rales present anteriorly and posteriorly in right chest Heart apex impulse in sixth interspace, by percussion outline to left 10.5 cm from midsternal line in sixth interspace, 3.5 cm to right in fourth interspace supracardiac dullness 6.5 cm at third interspace Sounds regular rapid of fair quality Second pulmonic sound is equal to the



Fig 4—Intermediate forms from peripheral blood of E W Wright's stain  $\times 1250$

second aortic Loud blowing systolic murmur at apex transmitted to axilla To and fro diastolic and systolic murmur at aortic area No thrill Pulses regular, equal, synchronous, of good volume and tension Liver enlarged, from fifth rib to 4 cm below costal margin in nipple line Slight tenderness

Entered hospital January 24 failing gradually Temperature from January 24 to 29 from 100 to 103 F, from January 29 to February 21, from 98 to 101 F February 22, weakness increased, pulse rapid Temperature increased to 105 F Respirations rapid and shallow February 23, death at 3 30 p m

Röntgen-ray showed mottling of right upper chest Conclusion tuberculosis or syphilis

*Laboratory Findings*—(exclusive of blood) Blood Counts, Table 2 and Chart 2 give data as to blood counts

Urine Normal color, acid, specific gravity 1.010 to 1.016, albumin, from slight trace to large trace, no sugar, diacetic acid or acetone, sediment, few granular casts

Stools Strong, positive guaiac test on two out of three examinations, once showed stringy clots of fresh blood

Wassermann Weakly positive during attack of pneumonia but twice negative since lung sign cleared up

Renal function (phenolsulphonephthalein) 10 per cent in two hours

Blood nitrogen 38 mg per 100 c c blood

Blood culture Negative February 10 Streptococci in both flasks February 22

Culture from bleb on hand No growth

Sputum January 25 Pneumococcus infection By mouse inoculation placed in Group IV

January 27 Pneumococci, few in numbers, continued to be present up to February 6, when the sputum showed almost pure culture of influenza bacilli  
February 15, influenza bacilli were present in great numbers

*Clinical Diagnosis*—Subacute bacterial endocarditis of aortic valve, streptococcus septicemia, recent bronchopneumonia

*Necropsy Summary*—Streptococcus septicemia, acute aortic endocarditis with large ulcerating vegetations on valve, soft hyperplastic spleen, moderate arteriosclerosis, slight hypertrophy and dilatation of heart, edema of lungs, chronic pleurisy, obsolete tuberculosis of apices of lungs



Fig 5—Smear from blood culture (E W) showing small, short chained streptococci  $\times 1250$

The striking features in the two cases presented were the similarity of the clinical findings and the presence of showers of unusual, phagocytic, mononuclear cells termed macrophages. The staining methods employed and the morphology of these cells will be discussed in some detail.

#### STAINING METHODS

In the case of E W (Case 2), Wright's stain was used throughout. In the case of C P (Case 1), Wright and Giemsa stains, the oxidase and peroxidase stains (diethyl-paraphenylene-diamine, alpha naphthol and benzidine-hydrogen-peroxide<sup>21</sup>) were employed. Cells of C P

<sup>21</sup> Fischel R. Wien klin Wchnschr 23 1557, 1910, Munch med Wchnschr 57 1203, 1910 (Quoted by Graham, G S. J M Research 34 15, 1918 as having priority in use of benzidine). Graham, G S. Benzidine as a Peroxidase Reagent for Blood Smears and Tissue. J M Research 34 15-24, 1918.

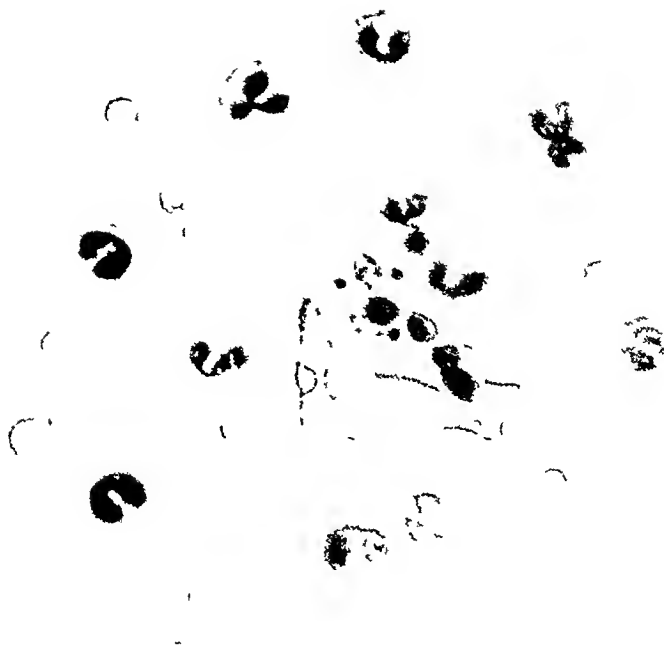


Fig 6—Large macrophage from peripheral blood of E W, showing phagocytosis and vacuolization Wright's stain



Fig 7—Intermediate forms from peripheral blood of E W (Wright's stain)



were also studied by a supravital staining method with neutral red and janus green Smith's stain<sup>22</sup> was used in an attempt to detect the presence of bacteria in the phagocytic cells

The technic of the supravital staining method used was that of Simpson,<sup>1</sup> developed from Pappenheim<sup>23</sup> and Rosin and Beberger<sup>24</sup> A saturated solution of janus green B in alcohol, in the proportion of three parts of the former to four parts of the latter, are mixed This mixture is then smeared, in the manner of making a blood smear, on smooth glass slides with perfectly regular surfaces The film of the dye must be even in distribution and without streaks, and with some experience the optimum thickness will be found The drop of blood to be examined is placed on a glass coverslip with a smooth, regular surface and inverted on the dye filmed slide The drop must be of proper size If the blood film is too thick inadequate staining results and makes proper observation of the cells difficult The preparations are rimmed with melted paraffin at once If the directions are followed closely, well stained living cells should be noted in a layer only one cell deep

#### MORPHOLOGY AND STAINING REACTIONS

The size varied from 10 to 80 microns inclusive of the small borderline forms and the cells with long phagocytic processes The ratio of cell volume to nuclear volume varied from 8:1 to 380:1 The nucleus was either round, oval, indented, polymorphonuclear or multiple (two, rarely three lobes) staining a bright purple with Giemsa and often definitely vacuolated The cytoplasm was generally heavily vacuolated and granular, containing phagocytized material of red cells, white cells and other unidentified nuclear material in all stages of disintegration Pseudopodia and bleblike projections were noted in the living forms but no ameboid motion was observed Stained with Giemsa the cytoplasm varied from deep blue to colorless, but was always packed with a large number of fine, reddish violet, azurophil granules with occasionally a scattering of coarse ones With Wright's stain the color of the cytoplasm and nucleus was similar but the finer details of the structure were not necessarily brought out The oxydase and peroxidase stain of the macrophages as well as the monocytes (Übergangsformen, transitional and large mononuclear cells

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22 Mallory, F. B., and Wright, J. H. *Textbook of Pathological Technique*, Philadelphia, W. B. Saunders Company, 1915

23 Pappenheim, A. *Einige Bemerkungen über Methoden und Ergebnisse sogenannter Vitalfärbungen an den Erythrozyten, Folia hematol. (Central Organ)* 9:90, 1910

24 Rosin, H., and Biberger, E. *Ergebnisse vitaler Blutfärbung*, *Deutsch med. Wchnschr.* 28:41-42, 1902



other than lymphocytes) gave a varying reaction from a heavy deposit to a few fine granules. By supravital staining with neutral red and janus green a heavy segregation apparatus of yellow red granules and numerous mitochondria granules were noted.

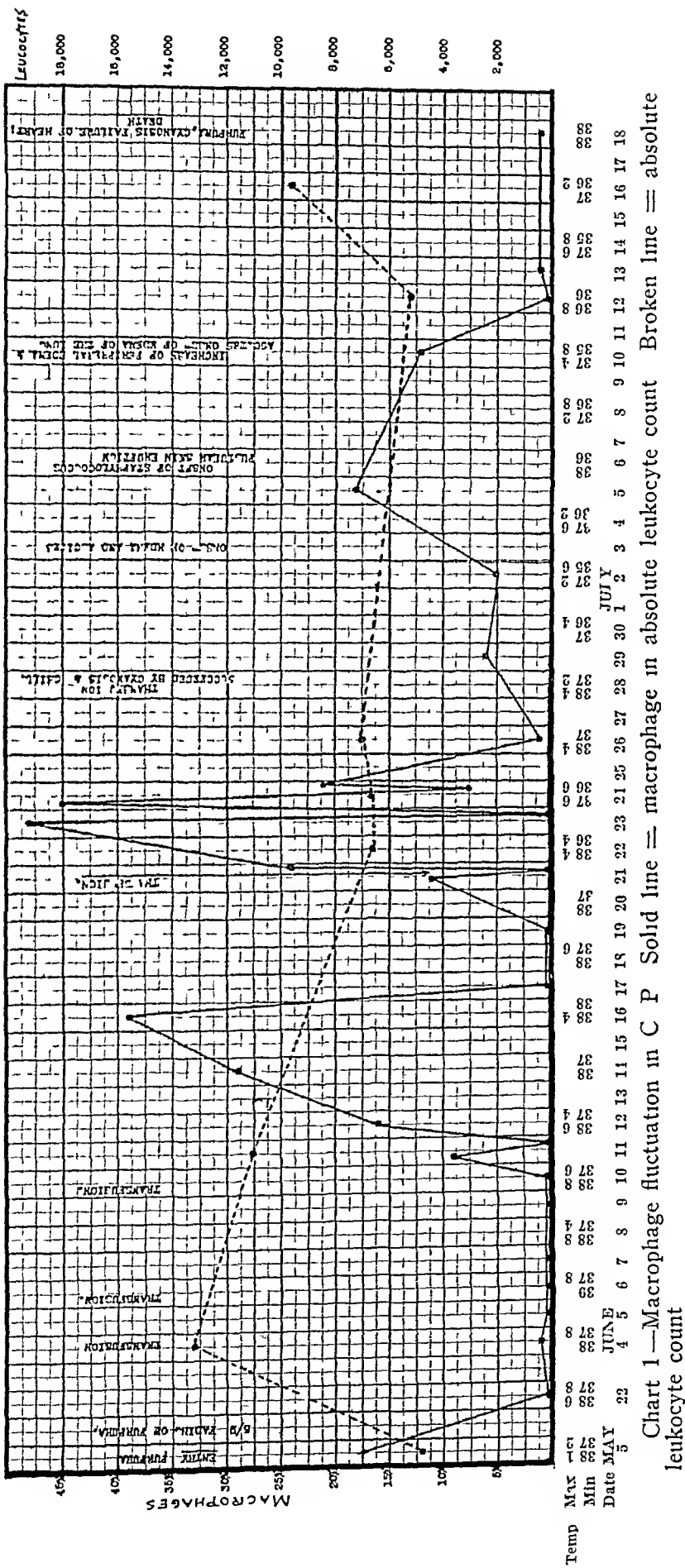
A Smith stain showed the presence of what appeared to be chains of streptococci in two out of one hundred macrophages studied. This observation should be taken reservedly because of the large amount of undifferentiated, phagocytized material noted in many of the larger cells.

#### BORDERLINE FORMS

It has been found by one of us<sup>1</sup> that during showers of macrophages produced experimentally in rabbits, there are forms of mononuclears which cannot be differentiated from the monocytes of the normal blood. These borderline forms have been termed intermediate cells. They occur in complete gradations from the well defined macrophage to the monocyte as determined by size, shape, color reaction and granulation with Giemsa stain, nuclear form, segregation apparatus and mitochondria by supravital staining. All of these criteria have been used in differentiating the cells but as a routine, films were stained with Wright's stain, which does not permit utilization of the segregation apparatus and fine azurophilic granulation as distinguishing points. However, the latter criteria have their chief value in separating the monocyte-macrophage group from the lymphocyte group of mononuclears. The increased size, the bizarre forms, the presence of vacuoles and organized phagocytized material in the former afford sufficient basis to distinguish the macrophages and intermediate forms from the lymphocyte group. The final distinguishing features, as brought out by supravital staining, are more conclusive, as the monocyte-macrophage group show marked fragility which may cause distortion of cells if the coverslip method is used in making film preparations. There is a remote possibility that the intermediate forms may be distorted monocytes, but clinically and experimentally there is evidence against this view, as will be discussed later.

#### MACROPHAGE FLUCTUATION

One of the striking features of the two cases studied was the marked, rapid fluctuations of the macrophages. This was particularly striking in the case of C P (Case 1), in which frequent observations were made over a period of two days. June 23 the percentage of these cells in the total leukocyte count fell from 38 to 1 in four hours, and June 24 it fell from 38 to 19 in an hour and a half and to 7.5 in the succeeding hour and a half (Table I, Chart 2). Other rapid fluctuations were noted. The fluctuations apparently had no relation to temperature, pulse or respiratory changes, time of day, digestion or disturbing



mental status (Charts 1 and 2) In the case of E W (Case 2), the absolute macrophage count paralleled the total leukocyte count except during the terminal leukocytosis This parallelism was the prevailing condition in the majority of cases presented in the literature In the case of C P the leukocyte count was never high, although the macrophages at times made up from 38 to 48 per cent of the total leukocytes The platelets in Case 1 (C P) did not grossly increase with the macrophages as was noted in Case 2 (E W) In the latter case the high leukocyte count and the high platelet count may have been due to increased bone marrow activity (Tables 1 and 2) The macrophages varied inversely with the bleeding time in the two cases

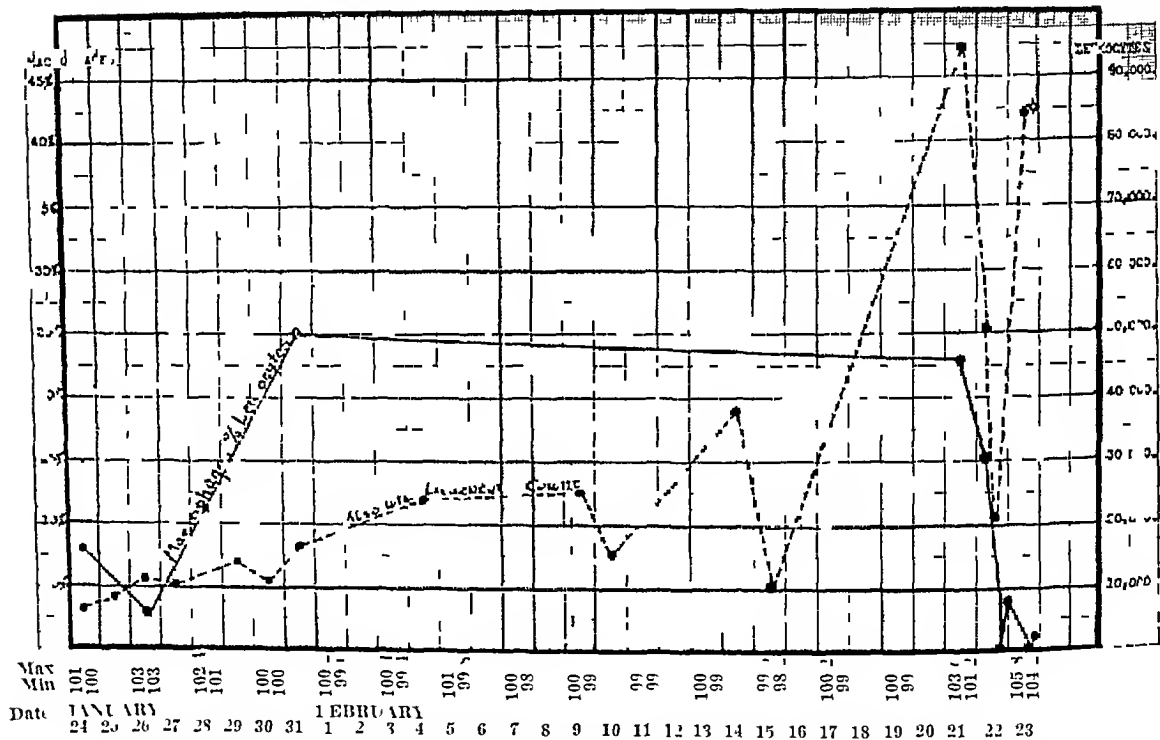


Chart 2—Macrophage fluctuation in E W Solid line = macrophages in absolute leukocyte count Broken line = temperature in degrees C

In the case of C P (Table 1) transfusions of citrated immunized blood in amounts of from 200 to 250 c c were employed as a therapeutic agent<sup>24</sup> The blood was obtained from a brother who had received subcutaneous injections of a killed culture of streptococcus viridans obtained from the patient's blood As will be noted from Chart 3, there was an increase in the relative number of macrophages three and fifteen hours after a transfusion It is suggestive that the introduction of even so closely related a foreign substance as whole citrated blood of the same biologic group (Moss—Group IV), whose content of antibodies as determined by agglutination was 1/50 of that of the

patient, should have stimulated the production of macrophages. This evidence, however, is minimized in view of the rapid daily fluctuations which are known to occur.

In both cases, as will be noted from Tables 1 and 2 and Charts 1 and 2, there was a decrease of macrophages at the time of death which was striking in the case of E. W.

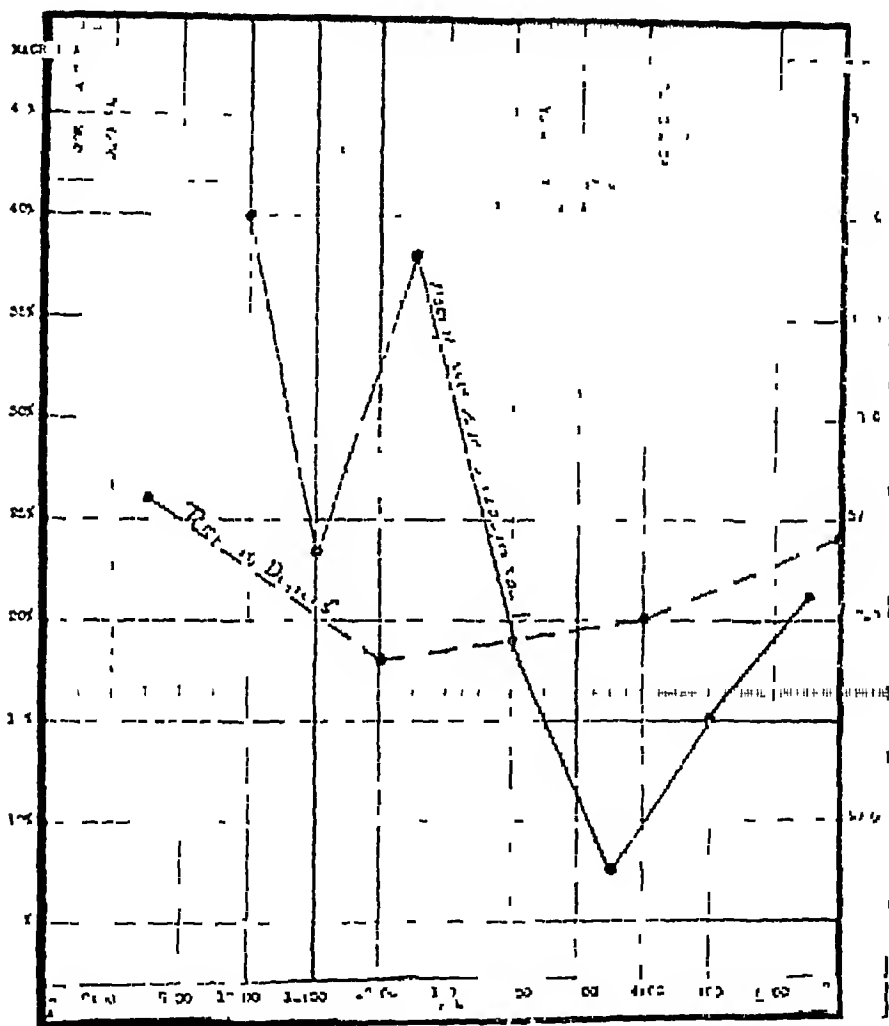


Chart 3—Daily macrophage fluctuation in C. P.

#### EXPERIMENTAL STUDIES

Simpson,<sup>1</sup> working with rabbits, showed that repeated injections of certain materials, with a common property of a colloid content,<sup>25</sup>

25 (1) Colloidal dyes (a) 1 per cent Niagara blue, N. A. C. Co., (b) lithium carmine, 5 per cent, (2) Coarser material held in colloidal state by protective colloids (a) red gold with sodium lysalbin, (b) India ink, (c) aqua-dag concentrated, (Acheson Oil Dag Co.), (d) lampblack, 5 per cent in 1 per cent gelatin, (3) protective colloids of group 2 (a) sodium lysalbin, (b) gelatin.

produce an excessive formation of macrophages. These cells were found chiefly in the lesser circulation, making up at times as much as 70 per cent of the total leukocyte count. In the peripheral blood, however, the macrophages were never more than 6 per cent and the size was decidedly smaller than that of the cells found in blood from the right heart. Rarely, an extremely large cell was found in the peripheral blood. Examination of the lungs showed the capillaries to be engorged with great numbers of these large cells, suggesting that the low percentage in the peripheral blood and their relatively small size depended on a filtration process in the lungs. There was also noted in the rabbit a rapid fluctuation in the number of these cells in the lesser circulation as well as in the peripheral blood, which suggests some other and possibly a specific mechanism for their removal other than a filter of fixed size.

Observations of the lungs of rabbits during a macrophage shower showed large cells with long attenuated processes extending through the capillaries. It is suggested that these cells have a subsidiary function in the production of platelets to compensate for the low platelet count in purpuric conditions in septicemias. This is in accord with the findings of Bunting,<sup>26</sup> who demonstrated the probability of the nonspecific origin of platelets through the squeezing off of processes of megalokaryocytes caught in the capillaries of the lung in Hodgkin's disease.

The possibility that the peripheral endothelium may be active in the production of macrophages is suggested by the findings in the case of localized leukocytosis described by Bartlett and the monocytosis, distal to a ligatured vein (Evans, Netausek).

The studies of Simpson point to the excessive formation of macrophages from the endothelium of certain organs, chiefly the liver, spleen and lymph nodes. Wright<sup>27</sup> suggests a similar secondary origin for blood platelets.<sup>28</sup>

#### DISCUSSION

We believe that the macrophage cells described in the two cases of subacute bacterial endocarditis presented were identical with those produced experimentally in rabbits by Simpson. This view is based

26 Bunting, C. H. Blood Platelets and Macrocytes in Hodgkin's Disease, *Bull. Johns Hopkins Hosp.* **12** 114-116, 1911.

27 Wright, J. H. The Histogenesis of the Blood Platelet, *Pub. Massachusetts General Hospital* **3** 1, 1910, *J. Morphology* **21** 263-278, 1910.

28 The following references also bear on this subject:

Levison, L. A. Unsuccessful Result Following Transfusion with Immunized Blood in Infectious Endocarditis, *J. Lab. & Clin. M.* **6** 191, 1921.

Nægeli, O. *Blutkrankheiten und Blutdiagnostik*, Ed. 3, Berlin u. Leipzig, Walter de Gruyter & Co., 1919.

on their resemblance as regards morphology, staining reactions, phagocytic properties, fluctuations and their disappearance at time of death

There is fairly conclusive evidence of the identical origin of the macrophages and monocytes from endothelium (Schilling,<sup>27</sup> Evans, Simpson,<sup>1</sup> Malloiy<sup>7</sup>) The work of Simpson points to their origin in the liver, spleen and lymph nodes with the discharge of these cells into the lesser circulation in response to certain stimuli Experimentally, the lung capillaries probably act as filters, allowing only the smaller cells to pass into the peripheral circulation The proportion of these cells to the total leukocyte count in the peripheral blood is higher than in experimental animals, suggesting also a peripheral origin This is in accord with the findings of other observers, especially in the localized leukocytosis of Bartlett and the observation of monocytes, peripheral to a ligatured vein (Evans, Netausek<sup>5</sup>)

The stimuli causing the production of macrophages and their release into the blood stream have been studied experimentally by Simpson It was shown that colloidal dyes, coarser material held in colloidal state by protective colloids, or protective colloids alone, by repeated injection, were capable of calling forth these cells The common property of these substances was the colloid content Thus we may assume that in addition to such substances as bacteria, foreign particulate matter, or chemical compounds, which are known to be capable of altering the absolute or relative blood count, the mere change in proportion of certain colloid elements, as the normal blood proteins, may stimulate the production or release of cells into the blood stream It is suspected that some such alteration of the colloid content in the blood may be the basis for the production of macrophages in these cases There is apparently no relation clinically between the fluctuations of these cells and those factors which cause definite variations in the leukocyte counts, such as fever, pain, digestion, embolic phenomena or bacterial showers, etc

Macrophages observed in the peripheral blood in man were generally smaller than in experimental rabbits, while the relative number was increased in the human observations These findings suggest that the cells liberated into the blood stream clinically are smaller because the mother tissues produce smaller cells in man or that a more protracted stimulus of a long continued infection calls forth smaller cells

Simpson discusses the possibility that the macrophages may engulf substances of certain limited sizes, and in such conditions as endocarditis these cells may be called out to handle such substances as the other phagocytes are incapable of dealing with

## SUMMARY

1 In two cases of subacute bacterial endocarditis, cells foreign to the normal blood stream were observed. They varied in size from 10 to 80 microns. The nucleus was round, oval, indented or multiple. These cells were markedly phagocytic with vacuoles containing engulfed cells, possibly bacteria, and unidentified material in all stages of disintegration. With Giemsa stain marked fine azurophilic granulation of the cytoplasm was observed. By supravital staining from six to seventy or more granules were noted in the segregation apparatus.

2 Intermediate forms varying from the cells just described to normal appearing transitional cells (monocytes) were observed.

3 Their fluctuations were rapid but without periodicity and varied from 0 to 48 per cent. They varied directly with the number of platelets (in the case of E. W. especially), inversely with the bleeding time and decreased at the time of death. There was an increase from three to fifteen hours after transfusion. The fluctuations were evidently not associated with changes of temperature, pulse, respiration, digestion or sudden changes of physical or mental status.

4 Certain deductions are made as to origin, cause of production and release, mode of removal and function of these cells through parallelisms of their behavior with similar cells produced experimentally.

5 It is hoped that certain criteria, such as segregation apparatus and azurophilic granulations, will be used on a large number of cases of mononucleatosis to aid in the recognition and classification of the group of cells herein discussed.

# PRIMARY CARCINOMA OF THE THYMUS \*

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Primary tumors of the thymus are uncommon. Primary carcinoma is an exceedingly rare variety of thymic new growths, hence any definitely established neoplasm of this type should be recorded. A few years ago I had the opportunity of studying a case of carcinoma of the thymus, arising from Hassall's corpuscles, with metastasis to many organs. It is from the clinic of Dr Henry A Christian, to whom I am indebted for his permission to use the clinical data.

## REPORT OF CASE

*History*—The patient, a salesman, aged 42 years, entered the hospital Sept 21, 1920, complaining of pain and stiffness in the lower part of his back. He was well up to June 1, 1920, when his back lay down felt stiff and sore on rising in the morning. After moving around an hour or two, this stiffness and soreness left, only to return in the evening. The diurnal remissions grew gradually shorter, and on June 10 he was so stiff and lame that he had to stop working. The right side of his chest and abdomen was tender on pressure and movement.

His condition was diagnosed muscular rheumatism by his local physician. His back was strapped and after seven days in bed he felt slightly improved. There was no fever, redness or swelling. Six treatments by an osteopath gave some relief and he went back to work August 1 and continued working until September 7.

Gradually increasing stiffness of the back and hips, and pain radiating from the back around the right side made work impossible. The pain was intense and continuous, keeping him awake nights. During the last four months he lost about 10 pounds in weight. In the last six days there has been marked hoarseness and for two days his hands have felt stiff.

*Physical Examination*—The patient is well developed and nourished and mentally clear. The pupils are prominent and there is bilateral, slow, rotary nystagmus. The optic disks and sight are normal. There are no cervical enlargements. Chest expansion is normal. The blood pressure is systolic, 110, diastolic, 70. Coarse piping rales are heard over the right side of the chest. The spine is very rigid, especially in the lower dorsal and lumbar regions. There is tenderness on attempt at movement but none under pressure. At the lower dorsal level there is a rather sharp kyphosis. Both legs are stiff at the hips and there is a bilateral Kernig sign. The knee jerks and Achilles reflexes are active and equal. The gait is very slow, the back being held rigid, and the hips move very little. Skin sensation is normal to rough tests.

Two weeks later the lungs were normal to percussion, respiratory sounds were exaggerated throughout. There was slight bronchial breathing at the right base behind. No signs of bone involvement, other than in the spine, were elicited. The patient's temperature was usually normal in the morning, rising to about 99.5 F in the afternoon. The urine was repeatedly negative for Bence-Jones protein. A surgical consultant regarded the condition as one of metastatic cancer, primary focus unknown, but said that if pyelograms did not

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\* From the laboratory of pathology of the Peter Bent Brigham Hospital, Boston.



indicate a hypernephroma the patient should be treated for tuberculosis, the slight fever corresponding better with cancer than with tuberculosis. The pycnograms were negative.

*Clinical Course*—The pain in the lower limbs became lancinating during the day and morphin was necessary. An orthopedic consultant made a diagnosis of Pott's disease of the tenth dorsal and third lumbar vertebrae. A plaster jacket was applied to the spine October 25, but the pain in the limbs became more severe. Temperature by mouth varied from 98 to 101 F. A bone graft operation was advised as being the most efficient and shortest means of producing immobilization of the diseased area.

November 8 the patient went home wearing his plaster jacket. He was to rest a week before returning for operation. He returned on the twenty-ninth with numerous bed sores and having lost much weight. December 9 an anterior shell was applied.

His temperature rose at times to 99.6 F, pulse, 130. The pain became gradually worse, requiring morphin two or three times in twenty-four hours. He soon became short of breath for the first time. His temperature fell to subnormal. Respirations were shallow and difficult. Death occurred Feb 9, 1921.

*Report of Roentgen-Ray Examinations* (Dr. Lawrence Reynolds)—Sept 24, 1920. Lumbar spine in an anteroposterior position shows a rotation of the fourth and fifth lumbar vertebrae. There is a slight scoliosis. The chest is slightly asymmetrical and the diaphragm is normal in contour, with the tracheal shadow a bit toward the right of the midline. Root shadows show considerable increase in their density. The type of increase is suggestive of glandular enlargement. There are some rather extensive areas of infiltration, far out in the lung fields on the left side, suggestive of possible metastasis.

September 30. Dorsal spine in anteroposterior and lateral positions shows definite destruction of the tenth dorsal vertebra with partial destruction of the third lumbar vertebra. The position suggests a metastatic rather than a tuberculous condition.

October 21. A reexamination of the spine over the region of the eleventh dorsal and the third lumbar vertebrae shows a small shadow of increased density about the eleventh dorsal which is possibly an abscess, but the third lumbar shows some increase in its destruction.

December 1. The spine still shows the destructive process in the tenth dorsal vertebra. The chest is slightly asymmetrical with definite rotation toward the right side. There is marked increase in the density of the root shadows over the previous examination, and the lung fields themselves are much more extensively involved. The type of involvement still suggests, from a roentgen-ray point of view, metastasis to the lungs with involvement of the mediastinal and hilar glands.

Dec 31. The chest shows rather extensive mediastinal involvement which is more marked than at the last examination.

Jan 7, 1921. Films of the dorsal spine in the anteroposterior and lateral positions show destruction of the tenth dorsal vertebra. The amount of destruction is about the same as at the last examination. The lung fields show no change since the last examination.

*Pathologic Report* (Necropsy performed one hour postmortem)—Anatomic Diagnoses. Carcinoma of the thymus with widely disseminated metastases, kyphotic deformity of the spine due to destruction of the tenth thoracic and third lumbar vertebrae by tumor, nephrolithiasis, left, acute appendicitis, hemorrhoids. There was metastasis to the lungs, liver, spine, suprarenals, chest and retroperitoneal lymph nodes.

*Mediastinum*. The organs in the anterior mediastinum are closely apposed to the sternum. There is general infiltration of the areolar and fatty tissues by a fibroid growth. Lying in the position normally occupied by the thymus is a mass extending from the level of the aortic ring to 1 cm above the sternoclavicular joints. Its inferior two-thirds appears to consist of cysts,

being fluctuant and of a dark color, which is transmitted through the thin capsule, suggesting, at first, markedly dilated veins. Incision permits the escape of a thin, brownish turbid fluid, under some pressure, disclosing a multilocular cystic growth, forming a chain of about four cysts which vary in size from 1 to 2 cm. They are lined with a white glistening membrane. Bordering these cysts is grayish-white tissue, very firm, and divided into fairly well defined lobules much in the manner of a thymus. This whole mass



Fig 1—Drawing of the condition found in the anterior mediastinum. The thymus contains many cysts which increase in a moderate degree its antero-posterior dimensions. The mediastinal fat has been dissected away.

strips away from the underlying structure much as the thymus does normally. It continues 1 cm above the level of the clavicle but is not adherent to the thyroid, which is quite normal. There are discrete, enlarged lymph nodes in the mediastinum lying posteriorly and beneath the medial ends of the

clavicles. Some of these are 2 by 1 by 1 cm. They are pale white, very firm, and consist almost entirely of tumor.

The pericardial cavity and heart are not remarkable. The great vessels are not involved in the tumor growth.

**Lungs.** Together the lungs weigh 1,675 gm. They are voluminous, with a moderate degree of emphysema of the anterior portions of the right and left upper lobes. The pleural surfaces are studded with grayish-white nodules averaging 6 mm in width, which project slightly above the surface. Many of these lie in dilated lymph channels and are covered with a thin layer of fibrin. In freeing the right lung some parenchyma infiltrated with tumor is torn away and left attached to the parietal pleura. On section both lungs show extensive involvement. About the right hilum firm white tumor tissue is concentrated in mass and spreads out into the more peripheral portions in a more or less fanlike manner. Peribronchial infiltration by tumor is conspicuous throughout both lungs. The lymph nodes at the hilum are markedly enlarged because of tumor.

**Spine.** The tenth thoracic vertebra is about 1 cm in thickness, having been practically replaced by a tumor growth which extends outward on both sides



Fig 2—Photograph of a section of the right lung showing the massive tumor infiltration proceeding outward from the hilum, also the perivascular and peribronchial metastases.

covering about one half of the anterior and lateral surfaces of the adjoining vertebrae, much in the manner of a mushroom. The body of the third lumbar vertebra is 2 cm in thickness and is also surrounded by a dense tumor growth extending to the right about 3 cm and practically covering the lateral surfaces of the second and fourth lumbar vertebrae. It does not appear to invade the intervertebral disks. The growth, both in the thoracic and lumbar levels, extends posterior to the bodies as well and there is considerable softening of the posterior lamellae of these vertebrae, but nothing of the nature of an abscess can be found. The tumor involving these vertebrae is pale white, very gritty, and definite spicules of bone are deeply embedded in it, even in the growth farthest away from the body of the vertebra itself.

**Microscopic Examination—Thymus.** The outlines of the organ can be made out in the sections, there being a distinct thin connective tissue envelop. Lobular divisions are fairly well defined in some sections, wide septums of connective tissue separating it into these units which are composed in great part of fat. In some of the lobules are foci of thymic lymphocytes, mononuclear

phagocytes (hemosiderin) and numerous eosinophils surrounding one or two normal appearing Hassall's corpuscles. Other similar foci show a proliferation of the cells of Hassall's corpuscles with the formation of bodies three or four times the size of the normal. Degeneration of the cells in these bodies follows the normal picture there being loss of nuclei, granulation and a sort of keratinization of the central cells. This is of progressively less prominence in the larger groups and assumes an entirely different aspect in the ones to be described. The proliferation of the epithelial cells forms bodies as much as ten times the size of the smallest groups and in these a central lumen appears and papillary ingrowths occur.

The cysts seen in the gross are lined by more or less flattened epithelial cells in layers of from two to four. No intercellular bridges are seen. Slight



Fig. 3—A longitucinal section through the spine showing the replacement of the tenth dorsal vertebra by a tumor which spreads out laterally in a mushroom-like manner. The vertebra has collapsed to about one-third its normal height.

recent hemorrhage has occurred in the walls and hemosiderin is present between the cells in some places. A thin layer of rather compact fibrous tissue surrounds the epithelium except where the cells have invaded it. Invasion of the surrounding areolar and fatty tissue from the concentric groups of epithelial cells and from the epithelium of the cysts is very striking in all the sections. The cells proceed in thick cords and are often have a narrow lumen.

Accompanying these outgrowths are many cells resembling small lymphocytes, numerous eosinophils and phagocytes filled with hemosiderin. These cells surround small Hassall's corpuscles which have begun to proliferate and

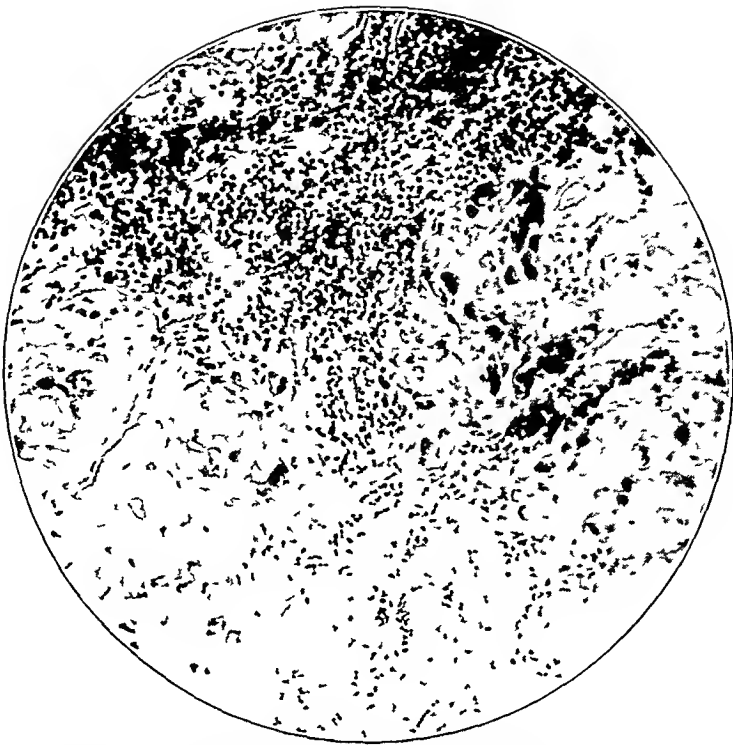


Fig 4—Photomicrograph of the thymus showing the malignant change in the epithelial bodies which in places tend to form cysts

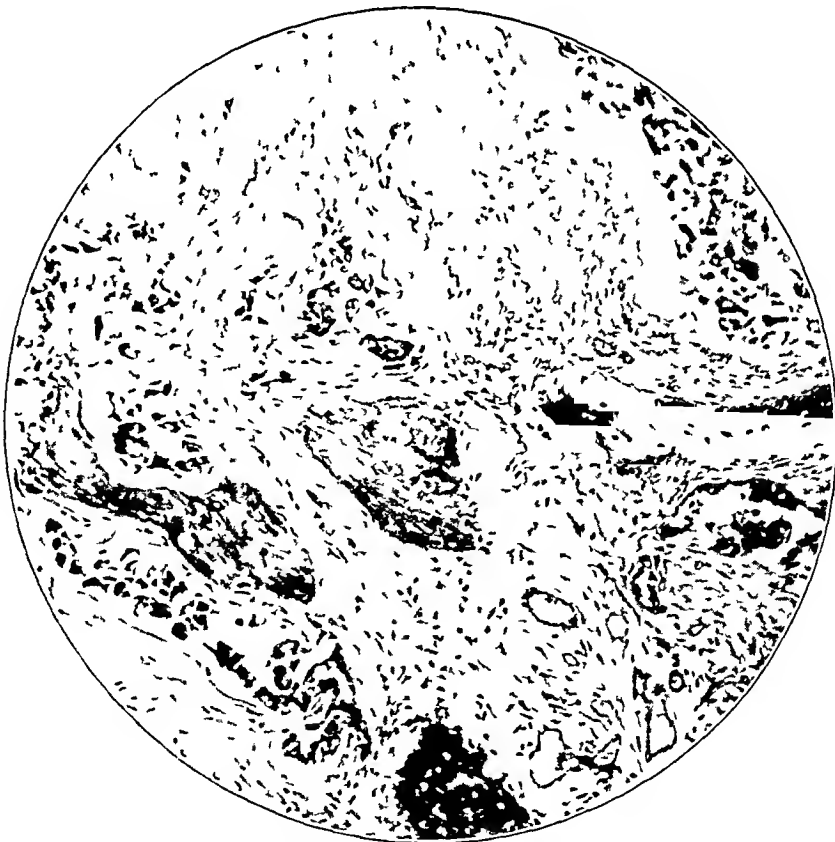


Fig 5—Photomicrograph of a section from the mushroom-like growth about the tenth dorsal vertebra

among them are slightly larger polyhedral cells with pale ovoid nuclei, probably the reticulum cells. These are comparatively few and show no transitions which might indicate that they are part of the neoplastic growth. The stroma of the tumor is composed of numerous blood vessels and connective tissue in small amount partly derived from the adventitia of the blood vessels. Invasion of both blood and lymph capillaries has occurred. Mitotic figures are numerous. As the tumor forms large conglomerate masses the cells assume the form of a syncytium with six to eight round nuclei, irregularly placed, the cytoplasm frequently appearing splashed with brilliant red, blue or both, with eosin-methylene blue staining. The architecture of the thymus is still unmistakable. The lobules while containing much fat have small Hassall's corpuscles surrounded by thymic lymphocytes. The various stages from the primary proliferation of the cells of the concentric bodies to the large epithelial tumor masses and epithelial lined cysts can easily be traced in the sections.

In the lung of chief interest are the peculiar degeneration changes in the tumor cells and a frequent intertolding of tumor cells in such a way as to suggest very strongly a Hassall's corpuscle. The nucleus is round or ovoid and large, being one third to one half the size of the cell and with one to three deeply eosin-staining nucleoli. The cytoplasm presents a bizarre coloring either deep blue or red or purple and in it are frequently present round, deeply colored bodies about the size of the nucleus usually with a halo or clear space about them. The nucleus is usually much shrunken or absent in the cells in which these bodies are found.

**Spine.** The mushroom-like growth on the side of the tenth dorsal vertebra consists of tumor in which are numerous trabeculae of new bone which undoubtedly arose from proliferation of the periosteum associated with extension of the tumor through it into the surrounding tissues. The tumor cells in these sections show the same peculiar staining properties and arrangement seen in the other metastases.

#### DISCUSSION

To better understand the development of tumors in the thymus gland a knowledge of its embryology is helpful. The thymus in man arises from the entoderm entirely, but in other animals it is from other sources, according to Zotterman.<sup>1</sup> In the mole it is purely ectodermic. In the pig it is of mixed origin. In the fowl isolated portions of striated muscle can be found, also cysts lined by ciliated epithelium. In man the thymus develops from two tubular outgrowths from the third pharyngeal pouches, although it is possible, according to Schafer,<sup>2</sup> that a part may be derived from the fourth pouch. The reticulum differs from that of a lymph gland in being essentially formed of a syncytium of branched cells which are not mesodermic but entodermic, being formed from the cells of the original epithelial tube and thus have a common origin with Hassall's corpuscles. Some writers have asserted that the thymic lymphocytes are also of entodermic origin (Stohr,<sup>3</sup> Bell<sup>4</sup>), but Hammar<sup>5</sup> and Maximow<sup>6</sup> found that the

1 Zotterman *Anat Anz* **38** 1911

2 Schafer *Quam's Anatomy, Textbook of Microscopic Anatomy* **2** 676, 1912

3 Stohr *Anat Heftte* **31** 1906

4 Bell *Am J Anat* **5** 1916

5 Hammar *Anat Anz* **26** 1905

6 Maximow *Arch f mikr Anat* **74** 1909

lymphocytes are brought to the developing gland and are not formed there primarily

Proliferation of the cells of Hassall's corpuscles is practically never seen in the normal thymus but it has been observed in a case of exophthalmic goiter reported by Soupault,<sup>7</sup> and in one of hemophilia by Acland.<sup>8</sup> Cysts of the thymus may arise in several ways. Persistence of the epithelial canals of the embryonal thymus is said to be a frequent cause of cysts in syphilitic infants (Ewing,<sup>9</sup> Pollossin and Piery,<sup>10</sup> and Chiari<sup>11</sup>). In Soupault's case there were also found multiple cysts lined by columnar epithelium. Dermoid cysts are reported by Hare, and a case of mixed tumor is recorded by Rolleston.<sup>12</sup> Hassall's corpuscles may be found in otherwise normal glands to have degenerated so as to form cysts barely visible to the naked eye, the "abscesses of Dubois." These cysts are probably comparable in many ways with epithelial cysts seen elsewhere, in the urinary tract for instance (Jacobson<sup>13</sup>).

Primary tumors of the thymus offer some difficulties in classification. Lymphosarcoma and malignant thymoma are terms commonly used to designate a tumor composed chiefly of cells resembling reticulum cells, although the small lymphocyte also is present in great numbers. This tumor usually penetrates the capsule and invades contiguous organs. These neoplasms of "lymphoid" type form the largest tumors taking origin in the thymus but they remain local or tend to keep within the bounds of the mediastinum. As a rule, this has been true also of the carcinomas, as most cases have shown no metastases, and no symptoms developed until the tumor had assumed considerable size.

To be correct, from the standpoint of embryology, the tumors definitely proved to arise from the cells of Hassall's corpuscles or the reticulum cells should be called carcinomas. The epithelium may be definitely pavement, cubical or cylindrical in type. The histologic picture of many thymus tumors is confused by the presence of many types of cells, lymphocytes, giant cells, eosinophils and plasma cells, in addition to cells of epithelial origin. Consequently, a diagnosis of carcinoma of the thymus is less frequently made than possibly it should be. Only two cases have appeared in the American literature, thirteen in the French and the rest have been described by the English and Germans, twenty-one, all told.

7 Soupault *Bull Soc Anat* **592** 1897

8 Acland *Proc Path Soc, London* **36** 491

9 Ewing *Neoplastic Diseases*, Philadelphia, W B Saunders Co, 1921, p 891

10 Pollossin and Piery *Prov med*, 1901, p 151

11 Chiari *Ztschr f Heilk* **15** 403, 1894

12 Rolleston *J Path & Bacteriol* **4** 228, 1896

13 Jacobson *Bull Johns Hopkins Hosp* **31** 122, 1920

According to Rubaschow,<sup>14</sup> who himself reported a mixed epithelial and lymphoid tumor in 1911, the first diagnosis of carcinoma of the thymus was made by Bristowe in 1854. The next cases appeared in 1867, and between 1890 and 1908 all the French cases were observed. The age incidence differs from that for epithelial neoplasms of other organs. Fifteen patients were of "cancer age," but the six others were persons from 18 to 22 years of age. Fourteen cases were in males, three in females, in four cases the datum as to sex is not available. The early involution of the thymus, as compared with other organs, and its peculiar interrelationships with the thyroid, and possibly other glands, place it in a somewhat different category and probably explain the relatively high percentage of tumors of the thymus in younger persons.

In three of the earliest observations no metastases are mentioned. Lung metastases were present in the cases of Cayley,<sup>15</sup> Le Tulle,<sup>16</sup> (Case 1), Ambrosini<sup>17</sup> (Case 2), and Symmers and Vance.<sup>18</sup> Direct extension into overlying lung tissue was noted by Paviot and Gerest,<sup>19</sup> and by Bruch,<sup>20</sup> who also found invasion of the mediastinal lymph nodes. In the second case of Le Tulle's there was growth into the superior vena cava and into the pericardium in those of Cayley and Ambrosini (Case 1). In only two instances was tumor found elsewhere than in the chest and this was in the second case of Ambrosini's, in which nodules were present in the liver, and in the case of Symmers and Vance. The case reported here is the second showing metastasis to the spine, Symmers and Vance having the first, and the invasion of other organs was more widespread than any case hitherto described.

The outstanding clinical features were the lack of local signs of thymus tumor and the predominance of symptoms referable to the destruction of several vertebrae. Roentgen-ray studies played an important part in the diagnosis and prognosis of the case. Despite the great bulk of lung tissue replaced by tumor, the patient had little respiratory distress until shortly before death. While he had also acute appendicitis, any pain or tenderness he might have had in the region of the appendix was probably masked by the constant severe pain caused by the tumor in and about the vertebral column. The ocular

14 Rubaschow. *Virchows Arch f path Anat* **106** 141, 1911 (quoting cases of Bristowe, Eriksen and Dersche).

15 Cayley. *Proc Path Soc Lond* **19** 53, 1867.

16 Le Tulle. *Arch gen de med* **2** 641, 1890.

17 Ambrosini. *These de Paris*, 1894.

18 Symmers, Douglas, and Vance, B. M., *Epitheliomata of Thymic Origin*, *Arch Int Med* **28** 239 (Sept.) 1921.

19 Paviot and Gerest. *Arch med Exper* **8** 699, 1896.

20 Bruch. *Prov med* **1** 267, 1904.



symptoms may have been due to cerebral metastases, but as the brain was not examined, this point could not be determined

The thymus tumor itself was comparatively small, especially in its anteroposterior dimensions and could not reasonably be expected to cause much mechanical inconvenience. However, invasion of the lymph and blood streams occurred early, the tumor being brought to the lungs by the pulmonary artery. The distribution of the tumor in the lungs is quite typical of this route of entry, i. e., massive growth about the hila, smaller nodules in the more peripheral zones, and further dissemination through the perivascular and peribronchial lymphatics to the pleura. In the lungs, tumor cells gained entrance to the pulmonary veins, thus reaching the systemic circulation, thence to the spine, liver and suprarenals.

This tumor was derived from the concentric epithelial groups of the thymus—the so-called Hassall's corpuscles. The reticulum cells played no recognizable part in making up the growth. Very little lymphoid tissue was present in the thymus, the lobules were still largely made up of fat which had replaced thymus tissue in the usual manner and probably at a normal time.

The degeneration phenomena in the cells of the tumor in the thymus and most of the metastases were very bizarre and might be said to be an exaggeration of the peculiar changes seen in the epithelium of normal thymus glands. There was also a tendency for the metastases to form structures resembling Hassall's corpuscles.

#### SUMMARY

1 The commonest tumors of the thymus gland are those of the so-called lymphoid type. Tumors derived from epithelial tissue are rare, although probably not so rare as the literature indicates. Such tumors can arise from (a) Hassall's corpuscles, or (b) the reticulum cells. This concept has a sound embryologic basis.

2 A study of a case of carcinoma of the thymus in a man, aged 42, with clinical, roentgenologic and pathologic findings in detail, is presented. Emphasis is laid on the difficulty of an antemortem diagnosis because of the manner of metastasis to lungs and spine, which simulated tuberculosis in several of its aspects.

3 From a pathologic point of view, of greatest interest are the peculiar degeneration changes in the nucleus and cytoplasm of the tumor cells in the thymus and in the secondary growths, changes which might be construed as an exaggeration of what occurs in normal Hassall's corpuscles. Also in the metastases the tumor cells sometimes tended to arrange themselves in groups suggesting Hassall's corpuscles.

# STOKES-ADAMS' DISEASE DUE TO GUMMA OF THE HEART \*

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Although heart block is no longer regarded as a rare disease, its association with a gumma of the heart is still of such infrequent occurrence as to merit the report of every case observed. In 1905 only three titles appeared in the Index Medicus on the subject of Stokes-Adams disease. In 1906 there are forty-six references to this disease, the result of interest excited by the work of Kent, His, Tawara and Erlanger. During the succeeding years a large number of articles on heart block appear. A total of 499 papers have been published from 1903 to 1922.

The number of such cases proved to be due to a gumma of the heart is quite small. Keith,<sup>1</sup> in 1909, collected seven cases, and Hirschfelder,<sup>2</sup> in 1913, also collected seven cases. I have been able to find only eleven cases in the literature up to 1922, those of Rendu,<sup>3</sup> Handford,<sup>4</sup> Keith and Miller,<sup>5</sup> Grunbaum,<sup>6</sup> Ashton, Norris and Lavenson,<sup>7</sup> Fahr<sup>8</sup> (also reported by Luce<sup>8</sup>), Vaquez and Esmein,<sup>9</sup> Heineke, Muller and Hosslin,<sup>10</sup> Robinson,<sup>11</sup> Bridgman and Schmeisser,<sup>12</sup> and Girdwood.<sup>13</sup>

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\*From the Department of Internal Medicine, University of Kansas School of Medicine

1 Keith, A. Albutt's System of Medicine 6 133, 1909

2 Hirschfelder, A. Disease of the Heart and Aorta, 1913, p 566

3 Rendu, M. Note sur un cas de syphilis du coeur accompagnee de poulslent permanent, Bull et mem soc med d hop de Par 12 381, 1895

4 Handford, Henry. Remarks on a Case of Gummata of the Heart, Brit M J 2 1745, 1904

5 Keith, A, and Miller, C. Description of a Heart Showing Gummatous Infiltration of the Auricular Ventricular Bundle, Lancet 2 1429, 1906

6 Grunbaum. Quoted by Hirschfelder, Footnote 2

7 Ashton, T G, Norris, G W, and Lavenson, R S. Adams-Stokes Disease (Heart Block) Due to a Gumma in the Interventricular Septum, Am J M Sc 152 1745, 1907

8 Fahr. Ueber die muskulare Verbindung zwischen Vorhof und Ventrikel (das Hissche Bundel in Normalen Herzen und beim Adams-Stokesschen Symptomkomplex), Virchows Arch f path Anat 188 562 1907

9 Vaquez and Esmein. Maladie de Stokes-Adams par lesion sclerogommeuse du faisceau de His (Herzblock), Presse med 15 57, 1907

10 Heineke, A, Muller, A, and Hosslin, H. Zur Kasuistik des Adams-Stokesschen Symptomkomplex und der Ueberleitungsstorungen, Deutsch Arch f klin Med 93 459, 1908

11 Robinson, G Canby. Gumma of the Heart from a Case Presenting the Symptoms of Adams-Stokes Disease, Bull Ayer Clin Lab, No 4, 1, 1907

12 Bridgman, E W, and Schmeisser, H C. Heart Block Caused by Gumma of Septum, Johns Hopkins Hosp Rep 18 90, 1919

13 Girdwood, R L. Case of Heart Block Due to Gumma, M J South Africa 16 183, 1921

The presence of a gumma in the heart associated with symptoms of Stokes-Adams disease is referred to by some earlier writers who failed through imperfect knowledge of the pathology of heart block to realize the significance of such association. Rendu's patient, who had a "permanent slow pulse," showed at necropsy a gumma the size of a pigeon's

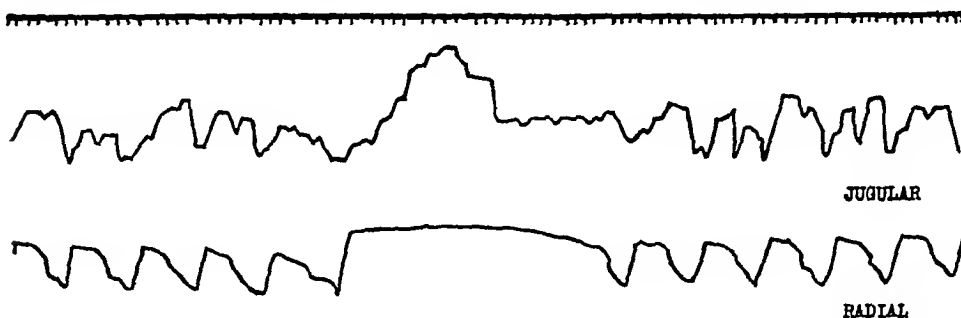


Fig 1—Pulse tracing made during an epileptiform attack

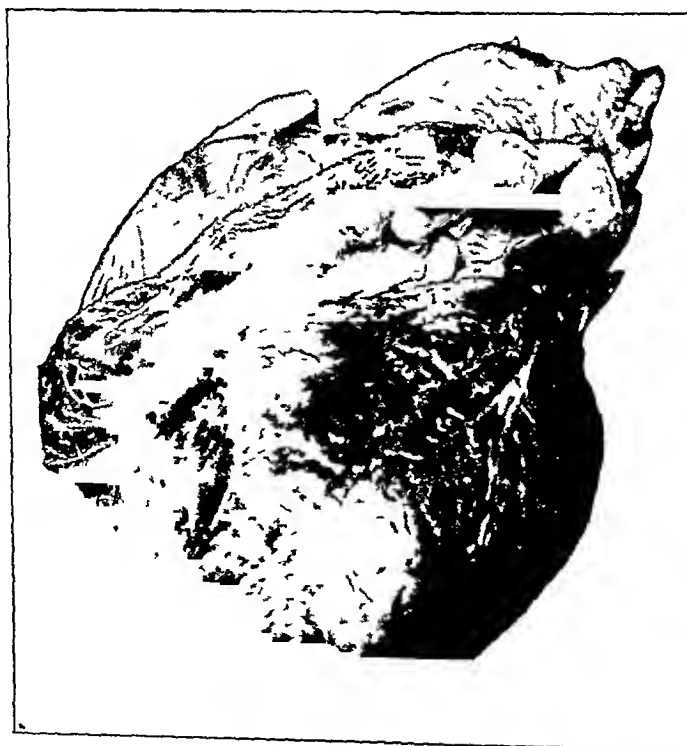


Fig 2—Photograph of heart with incision through the right ventricle. The gumma can be seen on the interventricular septum.

egg in the wall of the left ventricle. However, small granular kidneys were also found, and Rendu attributed the bradycardia to "uremic intoxication" of renal origin. Phillips,<sup>14</sup> in 1897, collected twenty-five

<sup>14</sup> Phillips, S. Syphilitic Disease of the Heart Wall, *Lancet* 1 223, 1897

cases of gumma of the heart, and he mentions syncope and epileptiform attacks as being frequent symptoms of the disease. Some of these cases were probably examples of Stokes-Adams' disease.

The case of heart block due to a gumma of the heart here reported is apparently the twelfth on record.

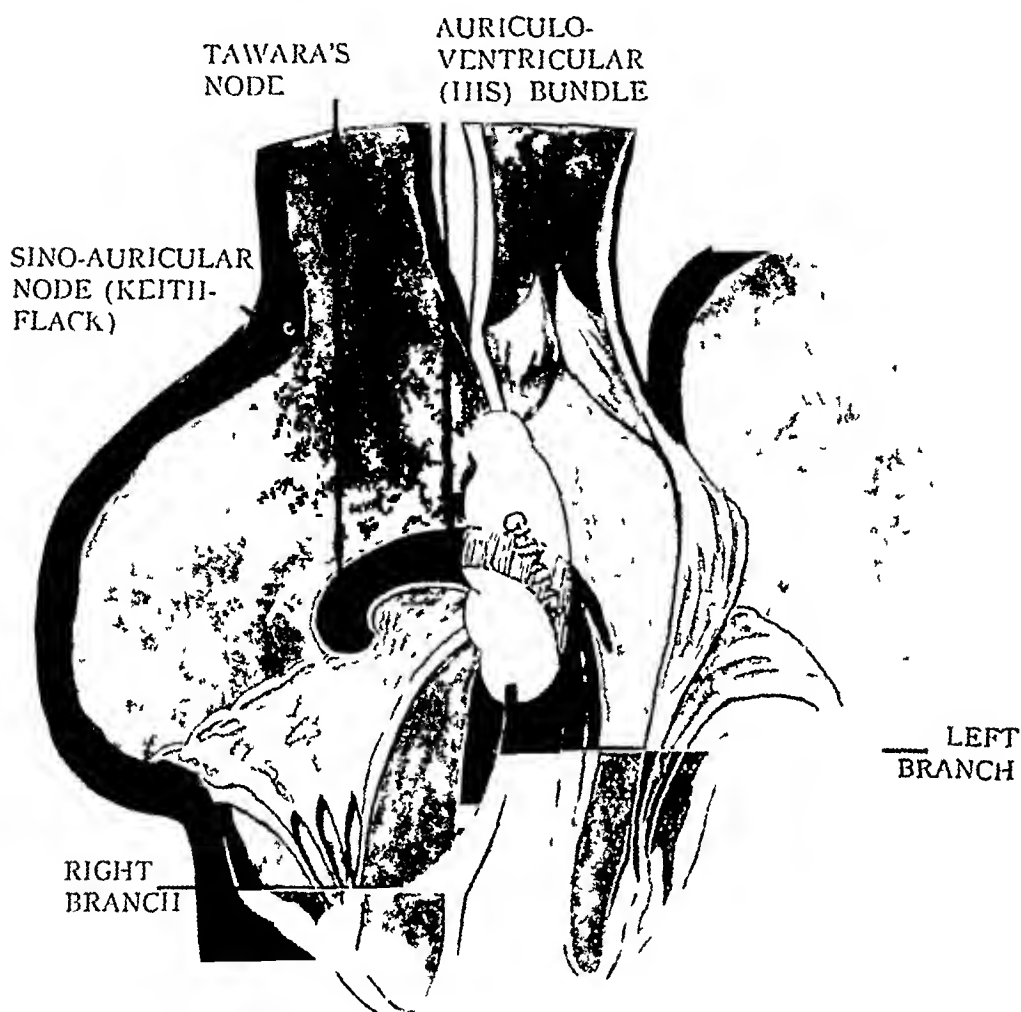


Fig 3—Sketch showing the position of the gumma (diagram of heart after Hirschfelder)

#### REPORT OF CASE

The patient was a man, aged 34, a farmer, who was admitted to the medical service of the Bell Memorial Hospital complaining of shortness of breath and weakness.

*Family History*—His father died of "heart trouble," the exact nature of which was unknown.

*Personal History*—This was negative. There was no history of rheumatic infection or of syphilis.

*Present Illness*—Two months before admission, the patient, while working in the field, suddenly became unconscious. This attack lasted about ten minutes. A few minutes following the attack he felt perfectly well and was able to continue his work. The next day he had a similar attack, and for six weeks he



Fig 4—Microscopic section through gumma (Bausch and Lomb obj 4 oc,  $\times 10$ )

had one or two such attacks a week. The past two weeks before admission the attacks became much more frequent, until at the time of admission he had several attacks a day.

*Physical Examination*—The heart was found to be enlarged, extending 14 cm to the left in the fifth interspace and 5 cm to the right in the fourth interspace. On auscultation, there was a blowing systolic murmur at the apex, and at the base there was a loud blowing systolic murmur and a somewhat softer blowing

diastolic murmur These murmurs were equally well heard at the aortic and pulmonary areas and almost completely replaced the heart sounds The pulse was of good volume, not collapsing and the rate varied from 42 to 60 per minute The radials were not thickened, and the blood pressure was 125 systolic and 80 diastolic The lungs were clear, there was no ascites or edema of the extremities The reflexes were normal

*Clinical Course*—While in the ward the patient had many epileptiform seizures, varying in number from eight to ten per day These attacks lasted from five to ten seconds The patient was unconscious, his face twitched, his eyes rolled up and were staring and his arms and legs were stiffly extended During these attacks the pulse could not be felt at the wrist, although the jugular pulse in the neck continued to beat

A tracing (Fig 1) taken during one of these attacks shows a complete absence of the radial waves while the jugular pulse records several *a* waves Both before and after this attack the tracing shows no evidence of any block, and the pulse rate was 60 per minute One tracing showed a two to one rhythm but all the other tracings taken showed a normal rhythm with periods of complete block corresponding to the patient's epileptiform attacks All tracings showed a prolongation of the *a-c* interval, the time usually being two-fifths of a second

*Laboratory Examination*—The blood cell count was red cells, 5,000,000, white cells, 10,000, hemoglobin, 90 per cent The urine was normal The Wassermann reaction was positive

*Treatment*—The patient was given hypodermics of atropin and strychnin but was not observed long enough to permit of drawing any conclusion in regard to the value of these drugs The patient died seven days after admission, during an epileptiform attack, and the necropsy was performed the following day by Dr Wahl

#### REPORT OF NECROPSY (BY DR WAHL)

The heart was enlarged and weighed 670 gm The coronary arteries showed no sclerosis On palpation of the heart indurated masses were felt at the bases of the aortic and pulmonary valves When the heart was opened, a yellowish mass measuring 5.5 by 2 by 2 cm was seen in the interventricular septum (Fig 2) extending up to the base of pulmonary valves It also extended into the base of the aortic valve and involved two of the aortic leaflets This mass bulged out into the cavity of the right ventricle and protruded also into the left ventricle It completely obliterated the triangular space, went directly across the right branch of the bundle of His, pressed on the left branch and extended nearly up to the auricular ventricular node (Fig 3) On cut section this mass was yellowish in color, somewhat granular and resembled a gumma

The anatomic diagnosis was gumma of the heart, aortic stenosis, aortic insufficiency, pulmonary stenosis, pulmonary insufficiency, hypertrophy and dilation of the heart, syphilitic aortitis

Microscopic sections taken from the mass (Fig 4) showed a typical gumma

This specimen resembles very much that described by Ashton, Norris and Lavenson, Robinson, Bridgman and Schmeisser and by Girdwood The large size of the gumma is noteworthy as are the combined aortic and pulmonary lesions produced by it The mitral systolic murmur described by Goodall as an almost invariable accompaniment of heart block was present here, but was not so marked as the systolic and diastolic murmurs originating at the base of the heart

# HYDROGEN-ION STUDIES VII EXPERIMENTAL NEPHRITIS IN RABBITS WITH MONOBASIC SODIUM PHOSPHATE \*

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Many studies of experimental nephritis are reported in the literature, notably those which concern the injection of the salts of the heavy metals, uranium and tartrates, into rabbits and dogs. There seems to be no mention of nephritis caused by the injection into rabbits of relatively large amounts of monobasic sodium phosphate. In the course of certain experiments with rabbits, injections of solutions of this salt were made and in the examination of the kidney tissue, necrosis of the cells lining the convoluted tubules and the loops of Henle was observed. Other experiments were made to confirm this observation, and in each instance depending in severity largely on the length of time that the rabbit was poisoned by the injections, there are necrotic changes in the cells of the renal tubules mentioned. Blood to be used for determining the hydrogen ion concentration and the carbon dioxide combining power was drawn from the heart through a sterile needle into a 10 c c defibrinating tube, all of the air being displaced. After defibrination by shaking, the hydrogen ion concentration of the blood was determined in a McClendon electrode vessel by the gas chain method. The carbon dioxide combining power of the whole blood was determined according to Van Slyke and Cullen.<sup>1</sup>

## PROTOCOLS OF EXPERIMENTS

The protocols for two typical experiments are given

EXPERIMENT 1—A rabbit weighing 2,470 gm was used. The urine was normal.

June 14, 1922 9 a m, bled,  $p_H$ , 7.57, carbon dioxide, 51.18 per cent by volume.

2 p m injected subcutaneously 10 c c 20 per cent solution of monobasic sodium phosphate.

June 15 9 30 a m, bled,  $p_H$ , 7.41, carbon dioxide, 48.29 per cent by volume.

11 a m 6 c c injected subcutaneously.

12 30 p m 8 c c injected subcutaneously.

2 30 p m Death, bled,  $p_H$ , 7.04, carbon dioxide, 27.10 per cent by volume. Urine contains a large amount of albumin, hyaline and granular casts, leukocytes, and a few red blood cells.

EXPERIMENT 2—A rabbit weighing 1,310 gm was used. The urine was normal.

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\* From the Pathological Laboratory of St. Luke's Hospital. Aided by the Winfield Peck Memorial Fund.

1 Van Slyke, D. D., and Cullen, G. C. Studies of Acidosis, I, J. Biol. Chem. 30: 289-346, 1917.

June 26, 1922 9 a m, bled,  $pH$ , 7.40, carbon dioxide, 53.93 per cent by volume

3 30 p m Injected subcutaneously 5 cc 20 per cent solution of monobasic sodium phosphate

June 27 9 a m 45 cc was injected subcutaneously The urine contains albumin, hyaline casts, and a few leukocytes

4 p m 45 cc injected subcutaneously

June 28 9 a m 5 cc was injected subcutaneously Urine contains albumin, many granular casts and cylindroids



Sketch illustrating necrosis of the convoluted tubules of the rabbit kidney following the injection of monobasic sodium phosphate solutions

June 29 10 a m, 75 cc injected subcutaneously

June 30 11 30 a m, 95 cc injected subcutaneously

July 2, 9 a m Urine contains a trace of albumin, a few granular casts and cylindroids

July 3 10 a m, 10 cc was injected subcutaneously

3 p m, 4 cc was injected intravenously Rabbit dead Blood carbon dioxide 12.14 per cent by volume



The changes in the kidney tissues, are most marked in the cells of the convoluted tubules, but are present also to a lesser degree in those of the loops of Henle. These changes are chiefly a necrosis of the epithelium, the cytoplasm of the cells becoming at first swollen and granular, then, with prolonged poisoning they become necrotic, so that only fragments of the basal portions and pyknotic nuclei of the cells remain. Within the lumen of the tubules there is a granular amorphous substance (precipitated albumin) in which there are occasional renal cells and polymorphonuclear leukocytes. The cells of Henle's loops and of the convoluted tubules contain fine dustlike droplets which stain with sudan III. These degenerative changes are like those observed by Wells<sup>2</sup> in rabbits the victims of tartrate poisoning.

#### DISCUSSION

Injury of the renal epithelium by the administration of the monobasic sodium phosphate probably is associated with the excretion of this salt by the kidneys. McNider,<sup>3</sup> Karsner<sup>4</sup> and others have observed an acidosis occurring with nephritis experimentally produced by salts of uranium. According to Fischer<sup>5</sup> acid bodies are important in a variety of pathological changes, particularly in nephritis. Karsner, however, regards the acidosis accompanying uranium poisoning not the direct cause of the renal irritation. Theoretically, an acidosis may be expected to follow the injection of an acid salt, and the results of such experiments may be considered the effect of the acidosis. However, the blood of a rabbit injected with 10 c c of a 20 per cent dibasic sodium phosphate solution changed in reaction from  $p_H$  7.40 to  $p_H$  6.80, the carbon dioxide combining power changed from 41.32 per cent by volume to 25.27 per cent, the urine contained albumin, casts and a large amount of sugar, and death ensued rapidly. The cell changes in the kidney sections of this rabbit also resemble those produced by the injection of the monobasic phosphate solutions. This suggests a much more profound disturbance in the general metabolism than merely the absorption and elimination by the kidneys of a salt injected subcutaneously.

The phosphate salts of sodium and potassium have a wide clinical use and that large amounts may be injurious to kidney tissue is suggested by the experiments reported here. It is known that with certain

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2 Underhill, F. P., Wells, H. G., and Goldschmidt, S. Tartrate Nephritis, *J. Exper. Med.* **18** 322-346, 1913.

3 McNider, Wm. deB. The Inhibition of Toxicity of Uranium Nitrate by Sodium Carbonate, etc. *J. Exper. Med.* **23** 171-186, 1916.

4 Karsner, H. J., etc. Studies of Uranium Poisoning. IV. The Relation of Acid Intoxication to Nephritis, *J. M. Research* **39** 177-187, 1918.

5 Fischer, M. H. Edema, a Study of the Physiology of Water Absorption by the Living Organism, New York, 1910.

patients the use of large amounts of phosphates is accompanied by the sudden appearance of albumin, casts and red blood cells in the urine. These manifestations of kidney injury may be regarded as the result of the use of the phosphate salts mentioned.

#### SUMMARY

The subcutaneous injection of monobasic sodium phosphate solutions causes in rabbits a necrosis of the cells lining the convoluted tubules and the loops of Henle.

An acidosis accompanies the injection of solutions of this salt.

Symptoms of an acute nephritis in patients receiving large amounts of phosphates may be due to changes in kidney tissue similar to those observed in rabbits.

# THE DILATATION OF THE PULMONIC AREA OF THE HEART AND ITS SIGNIFICANCE

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BOSTON

If the diagram representing the frontal view of the heart outlines, as shown on the fluoroscopic screen or by roentgenograms, is studied, several curves and depressions are noticed. The right side of the heart presents a single convex curve caused almost wholly by the auricle, the left side presents usually two curves, the superior curve caused by the aorta and the greater and inferior curve caused by the left ventricle. Between these two curves, situated usually between the second and third ribs, is a depressed line or concavity.

In this area, in abnormal conditions of the heart, the pulmonic artery and a portion of the auricle below it can sometimes cause two smaller curves instead of the normal depression. Or, frequently, a single marked curve is noticeable, so that the left side of the heart may show three noticeable curves instead of two. This third curve, if it covers the whole area, is caused by the dilatation of the pulmonic artery and auricle or to the pulmonary artery alone. This area is, then, commonly spoken of as the pulmonic area. On the right side there is never seen but one curve unless there is dilatation or an aneurysm of the ascending portion of the aorta.

In studying the changes in the heart three groups of cases must be kept in mind. The diagnosis of these cases may directly concern the heart or indirectly the lungs. By saying indirectly the lungs, I mean that the heart changes very frequently assist one in diagnosing the acuteness of the pulmonary lesion and sometimes assist in the prognosis of the lesion.

For some years I have been interested in the cardiac outlines in pulmonary conditions but not until the influenza epidemic of 1918, when I had the privilege of studying the cases at U S Army General Hospital No 16, did I realize the importance of the changes of the heart outlines in acute pulmonary conditions.

It is well known that dilatation of the right auricle occurs in pulmonary congestion and in children it is an important concomitant sign, but very little attention has been paid to the dilatation of the pulmonic area in pulmonary affections.

The dilatation of this area in cardiac diseases is well known. In mitral insufficiency and stenosis this area is markedly dilated. In pulmonary insufficiency complicating mitral disease, the pulmonic area forms a beautiful curve distinct in most cases from the auricle curve.

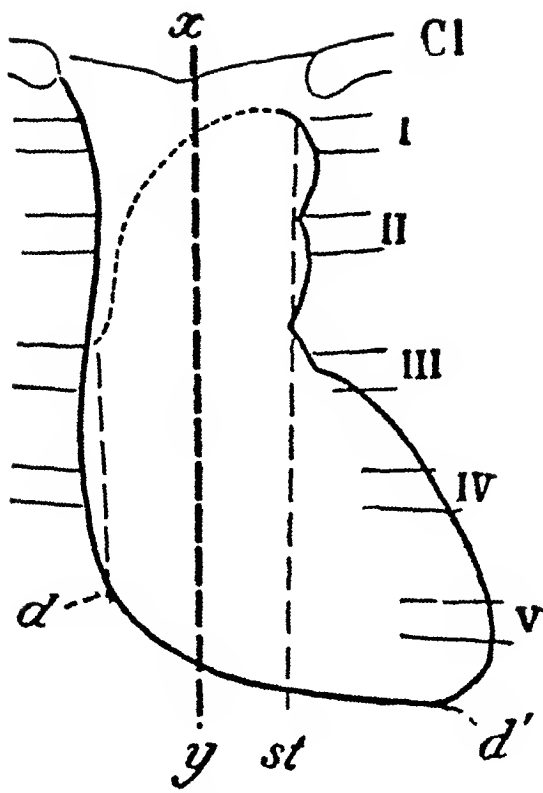


Fig 1—The normal cardiac outlines, with slight accentuation of the pulmonic curve, showing between the second and third ribs The aortic curve between the first and second ribs and the curve of the ventricle between the third and fifth ribs

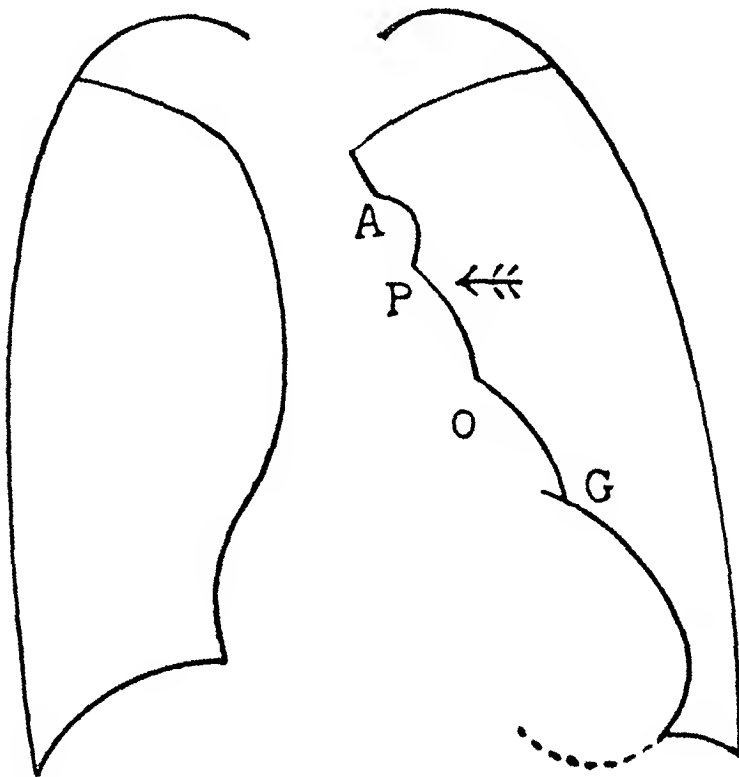


Fig 2—The abnormal cardiac outlines A Aortic curve P Pulmonic curve O Auricle curve G Ventricle curve The case represents a pulmonary insufficiency complicating mitral disease

which is also pronounced Stell, as quoted by Vaquez and Bordet, called attention to this and associated changes and states that mitral lesions, especially stenosis, could provoke, following increase of pressure in the smaller vessels, an insufficiency of the pulmonary orifice of functional nature. So also in congenital pulmonary stenosis and in conditions of interventricular perforation and in other cardiac conditions. Such conditions, however, have no relation to any extent to pulmonary conditions, with the exception of cardiac pulmonary insufficiency and myocarditis.

In pulmonary conditions this pulmonic curve very early becomes pronounced. Some time ago I<sup>1</sup> pointed out that in influenza "the heart shows a slight dilatation of the right auricle and, to a less extent, a



Fig. 3—Dilatation of the pulmonic area in a child without discernible cause

slight dilatation of the pulmonic area," and in pneumonia "two associated changes occur very early which are of great interest and importance. Invariably, as early as the changes occur in the hilus, there is seen in the heart a marked and acute dilatation of the pulmonic area." During the epidemic, necropsy findings constantly included the observation of the noticeable dilatation of the right auricle, but, no notice, or little, was apparently taken of the pulmonic area.

It can be accepted, therefore, that dilatation of the right auricle and to a less extent the pulmonic area, is known to be associated with acute pulmonary conditions.

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<sup>1</sup> Honey, J. A. Influenza and Bronchopneumonia, *Am J Roentgenol* 6: 266 (May) 1919.

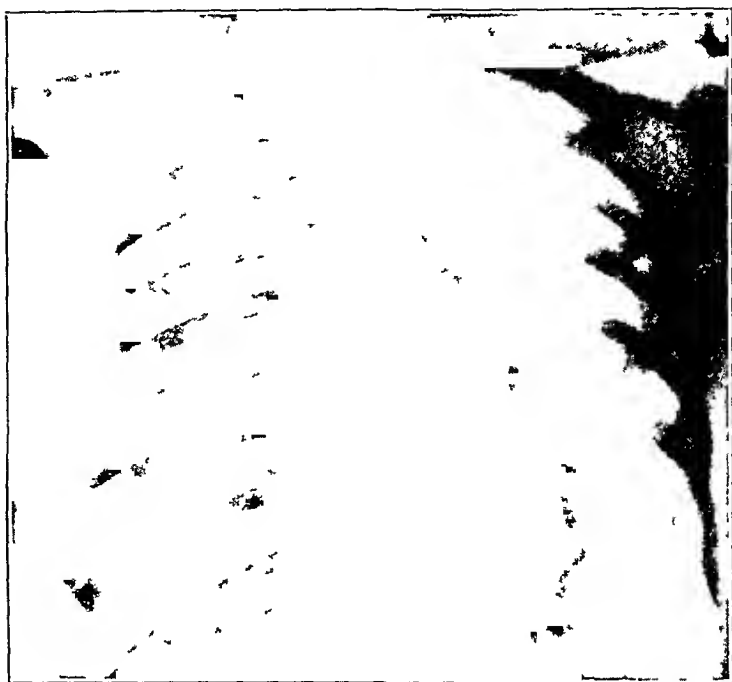


Fig 4—Dilatation of the pulmonic area of a child without discernible cause



Fig 5—Dilatation of the pulmonic area in a child without discernible cause

The third general class of cases of dilatation of the right auricle is associated with pulmonary tuberculosis. In many of these cases I have seen some dilatation of the pulmonic area, especially in children. In a series of twenty-five cases, in children under 16 years of age, which were being studied for tracheobronchial gland changes, and in which only two cases of cardiac disease occurred, I have noticed dilatation of the pulmonic area in thirteen. The cause of this cannot at the present time be considered to be pulmonary congestion, as in most cases there was no apparent congestion. It might be assumed at this time that gland pressure and congestion may probably be an associated cause.

It is well known that some dilatation of the heart and of the pulmonic area can be produced physiologically by repeated coughing without inspiring, but why dilatation of the pulmonic area occurs when there is apparently no pulmonary stress is a question that needs studying. It is well worth while to consider this concomitant sign in interpreting roentgenograms of chests. It may be transitory and in many cases it is progressive.

Recently Bishop<sup>2</sup> published an article in which he quotes Vaquez and Bordet<sup>3</sup> as follows: "Vaquez and others have come to our rescue in their observations in this one particular, namely, that a very distinct dilatation in the region of the conus, meaning an enlargement of the pulmonary artery, showed no corresponding post-mortem condition by the methods employed in such work up to the present time. In fact, the examination of the right side of the heart and pulmonary circulation is, as a rule, carried out carelessly." Further on in this article, the author states, that "the fluoroscope usually shows besides a centrally located heart shadow, a fairly definite predominance in the region of the conus." It is evident that the author in making a diagnosis of "infantile heart" obtains part of his evidence from the roentgenogram showing a dilatation of the pulmonic area, for besides his statements he concludes his article thus, "the illustration is a typical example of an infantile heart in an adult."

I can only say that without precise cardiac measurements, or positive absence of pulmonary changes or absence of postmortem proof, the "infantile heart in adult life" cannot be considered seriously. This is purely from the roentgenographic point of view of the abnormal cardiac outlines.

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<sup>2</sup> Bishop, L. F. *The Infantile Heart in Adult Life*. Boston M. & S. J. 187 23 (July 6) 1922.

<sup>3</sup> Vaquez and Bordet. *The Heart and the Aorta*, translated by James A. Honey and J. Macy.

# OBSERVATIONS ON THE BLOOD GASES IN AURICULAR FIBRILLATION AND AFTER THE RESTORATION OF THE NORMAL MECHANISM \*

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The object of this investigation was to determine what changes take place in the gases of the arterial and venous blood when the cardiac mechanism reverts from auricular fibrillation to the normal mechanism. There has been no report of similar studies in the literature, and, indeed, such studies were hardly possible, except in the uncommon condition of paroxysmal fibrillation, until quinidin sulphate was found to bring about the restoration of the normal mechanism in auricular fibrillation.

In the studies which Harrop<sup>1</sup> made of the blood gases there are reported two cases of auricular fibrillation with determinations of the gases of the arterial and venous blood during decompensation and after the patients became compensated. Peters and Barr<sup>2</sup> give the carbon dioxide absorption curves and blood gases in two cases of auricular fibrillation in their studies on cardiac dyspnea. Lundsgaard<sup>3</sup> has included several cases of auricular fibrillation in his report on the oxygen of the venous blood in patients with compensated and decompensated circulatory disturbances. Barach<sup>4</sup> has studied oxygen therapy in two cases of auricular fibrillation. In none of these cases, however, is there a return to the normal mechanism.

All the patients included in this study were put to bed on admission and, if there were any signs of cardiac failure, a standard tincture of digitalis<sup>5</sup> was administered up to the point of maximum benefit before the quinidin therapy was begun.

Control samples of arterial and venous blood were usually taken after digitalization. The patient was then given a preliminary dose of 0.2 gm quinidin sulphate to determine any idiosyncrasy. If there was no untoward reaction to the preliminary dose, the patient was started on larger doses (0.4 gm), given from three to five times a day. The

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\* From the Physiological Division of the Medical Clinic of the Johns Hopkins University and Hospital.

\* Working under the tenure of the William Bingham Fellowship in Medicine.

\* Abstract read before the American Society for Clinical Investigation, Washington, May, 1922.

1 Harrop, G. A. J. *Exper. Med.* **30** 241, 1919.

2 Peters, J. P., and Barr, D. P. *J. Biol. Chem.* **45** 559, 1921.

3 Lundsgaard, C. J. *Exper. Med.* **27** 179, 199, 219, 1918.

4 Barach, A. L. *Arch. Int. Med.* **28** 367 (Sept.) 1921.

5 One c.c. of the tincture is equivalent to 1 cat. unit.



drug was continued until there was some indication for discontinuance. The arterial and venous samples of blood were obtained after the onset of the normal mechanism. Control galvanometric records were frequently taken.

#### METHODS

The arterial and venous samples were drawn without stasis under liquid petrolatum as described by Stadie<sup>6</sup> for arterial blood and by Lundsgaard<sup>7</sup> for venous blood. In a total of about one hundred arterial punctures there was no untoward effect, in most instances the patients said the arterial puncture did not cause any greater discomfort than the venipuncture. Procaine was used only in a few cases. Usually, the arterial blood was drawn before the venous blood, but in the case of persons in whom the most accessible vein and artery were in the same arm, the venipuncture was done first in order to avoid the stasis brought about by pressure applied after the arterial puncture. In some persons the radial artery was used, and in others the brachial artery. The patients in whom both the radial and the brachial artery were punctured preferred the brachial puncture. One of the veins at the bend of the elbow was used for the venous blood. The arterial and venous samples were drawn within from three to five minutes of each other. The venous blood was sometimes drawn in a syringe<sup>8</sup> and at other times in a pipet<sup>7</sup>. The analyses were done in duplicate immediately after the blood was drawn. The earlier analyses were done with the original type of Van Slyke apparatus, using the Van Slyke methods for determining the carbon dioxide<sup>8</sup> and oxygen<sup>9</sup> of the whole blood. Later the "giant" Van Slyke apparatus was used, the pipet of which is twice the length and approximately one half the bore of that of the original apparatus, and is calibrated to 0.01 c.c. instead of 0.02 c.c. The Van Slyke and Stadie<sup>10</sup> method for determining oxygen and carbon dioxide in the same sample was used. In all analyses the new corrections for the oxygen and nitrogen physically dissolved in the blood were used. When oxygen and carbon dioxide were done on separate specimens of blood, the order of analysis was as follows: venous carbon dioxide, arterial carbon dioxide, venous oxygen, arterial oxygen and oxygen capacity of the arterial blood. When the combined method was used, the venous blood was analyzed first, then the arterial blood and lastly the oxygen capacity was determined.

The samples of blood were drawn at least two hours after the previous meal, after the patient had been lying at absolute rest for half

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6 Stadie W. C. *J. Exper. Med.* **30** 215, 1919.

7 Lundsgaard, C. *J. Biol. Chem.* **33** 133, 1918.

8 Van Slyke, D. D. *J. Biol. Chem.* **30** 347, 1917.

9 Van Slyke, D. D. *J. Biol. Chem.* **33** 127, 1918.

10 Van Slyke, D. D., and Stadie, W. C. *J. Biol. Chem.* **49** 1, 1921.

an hour or longer. After the patients left the hospital they returned for frequent observations, the same precautions being taken in obtaining the samples. Pulse and respiration rates were recorded during both the arterial and venipunctures. The blood pressure, galvanometric record and vital capacity were taken either just before the rest period or immediately after the blood was drawn.

During fibrillation the average systolic blood pressure was determined after the method of James and Hart<sup>11</sup>. The normal vital capacity was calculated from West's formula<sup>12</sup> according to which the normal vital capacity is 2.5 litres per square meter of body surface area in men, and 2 litres per square meter of body surface in women. The body surface area was estimated from the height-weight chart of Du Bois and Du Bois<sup>13</sup>. The vital capacity is recorded as percentage of the normal

#### GROUPING OF CASES

Fifteen cases of auricular fibrillation have been studied. Fourteen of these patients received quinidin sulphate, in twelve there was reversion to the normal mechanism. The cases have been divided into the following groups:

GROUP I—Nine cases studied during fibrillation and after the restoration of normal mechanism.

GROUP II—Two cases, which were studied after reversion to normal mechanism, but in which no analyses were made in the presence of fibrillation.

GROUP III—Four cases studied during fibrillation but not during normal mechanism.

#### REPORT OF CASES

##### GROUP I

CASE 1 (2) (Tables 1 and 2)—Patient was a female, white, aged 63 years, who was admitted to the hospital, Nov 2, 1921. She was discharged, improved, Dec 7, 1921. Mechanism was normal.

*History*—Three years ago patient had her first attack of cardiac failure. Three subsequent attacks of cardiac failure occurred.

*Examination*—There was slight edema of the feet and ankles; no dyspnea, no cyanosis, a few râles at the bases posteriorly, the liver was enlarged. The heart was slightly enlarged, the rhythm was totally irregular, a systolic murmur heard at the apex was transmitted to the axilla. A systolic murmur was heard in the second right interspace, and faintly heard in the neck vessels. The Wassermann test was negative.

*Diagnosis*—Arteriosclerosis, hypertension, myocardial insufficiency, auricular fibrillation.

*Treatment*—Nov 3 and Nov 4, 1921, the patient received digitalis, bringing the heart rate down to 64, with a pulse deficit of 4. November 8, the patient reverted to a normal mechanism. November 11, she reverted to fibrillation, and

11 James, W. B., and Hart, T. S. *Am J M Sc* **147** 63, 1914.

12 West, H. P. *Arch Int Med* **25** 306 (March) 1920.

13 Du Bois, D., and Du Bois, E. F. *Arch Int Med* **17** 863 (June) 1916.

November 13 the normal mechanism was again restored. The patient was discharged with a normal rhythm, which was still present when she was last seen in May, 1922.

This case shows an increase in the oxygen saturation<sup>14</sup> of arterial and venous blood and a diminution of the coefficient of utilization with the onset of the normal mechanism, which indicates an improvement in the blood flow. There was a persistent anoxic anoxemia,<sup>15</sup> except on one occasion. There was no apparent cause for this arterial anoxemia. Dec. 19, 1921, when the arterial blood was 100 per cent saturated, the venous saturation was 94 per cent, and the venous blood was as bright red as the arterial. The oxygen consumption and the oxygen capacity were both decreased. A progressive improvement in the vital capacity was seen. The cause for the venous (stagnant) anoxemia December 5, in the presence of the normal mechanism, is not clear, but it was felt at the time that the patient probably had been going beyond her cardiac reserve and might be on the verge of cardiac failure, although she showed no clinical signs of failure. There was great subjective improvement in the patient with the normal mechanism and since leaving the hospital she has been doing her own work without the occurrence of dyspnea or edema.

**CASE 2 (9) (Tables 1 and 2)**—Patient was a man, white, aged 29 years whose first admission was Nov. 7, 1921. He was discharged, Dec. 3, 1921, with a normal mechanism. Second admission was Feb. 28, 1922. Patient was again discharged, March 11, 1922, with a normal mechanism.

**History**—Patient complains of lack of vitality and endurance. He had influenza in 1918. Since then he has had his present symptoms. Oct. 15, 1921, an electrocardiogram showed auricular fibrillation.

**Examination**—There were no signs of cardiac failure. The heart was not enlarged; the rhythm was totally irregular, with the apex rate 60, and a pulse deficit of a few beats. There were no murmurs. The Wassermann test was negative.

**Diagnosis**—Chronic myocarditis, slight myocardial insufficiency, auricular fibrillation.

**Treatment**—Digitalis was not necessary. November 10, administration of quinidin sulphate was begun and the patient reverted to normal mechanism the same day with no subjective improvement. November 18, the patient reverted to fibrillation and November 20 normal mechanism was again restored, and was present on his discharge. December 16, the patient had reverted to fibrillation. He was readmitted with an apex rate of 72 and a pulse deficit of 12. Quinidin sulphate administration was begun, and the patient reverted to normal mechanism, March 1. He was discharged with a normal mechanism, but returned again fibrillating and was given quinidin daily. March 24, fibrillation was still present and the dose of quinidin was increased. March 31, normal mechanism was found which was still present April 10 when the patient asked to be allowed to discontinue the use of quinidin.

<sup>14</sup> Arterial saturation and venous saturation in the text refer to the per cent arterial oxygen saturation and per cent venous oxygen saturation, respectively.

<sup>15</sup> Barcroft. I. *Lancet* 1:487, 1920.

This is a case of probable rheumatic heart disease, with as yet very slight structural change, but functionally there is some impairment of cardiac reserve. This case shows an increase in the venous oxygen saturation and a decrease in the coefficient of utilization with each fluctuation from auricular fibrillation to the normal mechanism, indicating an improvement in the circulation. There is a decrease in the arterial oxygen saturation after the onset of the normal mechanism, with the first two reversion from fibrillation to normal mechanism, but in the third reversion the arterial saturation rose to 100 per cent. Nevertheless, the patient showed no subjective improvement with the normal mechanism, although the discomfort caused by the quinidin sulphate might have masked any such improvement. It is interesting to note the extremely high vital capacity of this patient, and its rise following the onset of normal mechanism. From Table 1 it is seen that the oxygen capacity diminishes with the onset of the normal mechanism, increases when fibrillation begins and decreases each time with the normal mechanism. The high hemoglobin content during fibrillation is noteworthy. The oxygen consumption diminished with the onset of the normal mechanism.

**CASE 3** (Tables 1 and 2)—Patient, male, white, aged 77 years, was admitted Nov. 30, 1921, and discharged, Dec. 14, 1921, improved and with a normal mechanism.

*History*—Auricular fibrillation was discovered in a routine physical examination made July 8, 1919. He has had no acute cardiac failure. He had received a small amount of digitalis just before admission.

*Examination*—There were no signs of cardiac failure, but signs of senile emphysema. The heart was not enlarged, the rhythm was totally irregular. At the apex, the first sound was accompanied by a soft systolic murmur. A pre-systolic gallop was present. The radials were tortuous and thickened.

*Diagnosis*—Arteriosclerosis, emphysema, myocardial degeneration, auricular fibrillation.

*Treatment*—Digitalis was not necessary. The patient reverted to normal mechanism, December 5. December 9, the electrocardiogram showed auricular flutter. December 11, normal mechanism was again present. The patient was discharged with a normal mechanism.

This patient was much improved subjectively by the reversion to the normal mechanism. With the change to the normal mechanism the venous saturation increased, and the coefficient of utilization diminished. There was a decrease in the arterial saturation immediately after reversion to the normal mechanism, which later returned to the normal level. The patient's emphysema did not prevent normal saturation of blood with oxygen in the lungs, except on two occasions when there was a slight anoxic anoxemia. The oxygen consumption was decreased, the oxygen capacity was first slightly increased then appreciably diminished and later when iron was administered, it increased again. This

TABLE 1—CHANGES IN BLOOD GASES IN AURICULAR FIBRILLATION AND AFTER REVERSION TO NORMAL MECHANISM CASES OF GROUP I

Case No	Diagnosis	Date	Mechanism	Vital Capacity, per Cent Normal	Oxygen Content		Oxygen Saturation		Coefficient of Utilization, per Cent	Oxygen Consumption, Volume per Cent	Oxygen Capacity, Volume per Cent	Hemoglobin, per Cent	Carbon Dioxide		Blood Pressure
					Arterial, Volume per Cent	Venous, Volume per Cent	Arterial, per Cent	Venous, per Cent					Arterial, Volume per Cent	Venous, Volume per Cent	
1 (2)	Arteriosclerosis, hypertension, myocardial insufficiency, auricular fibrillation	11/7/21	Aur Fibr	58	11.49	8.43	84.3	61.9	22.4	3.06	13.63	73.6	42.64	47.49	184 mm
		11/8/21	Normal	58	10.75	8.66	91.8	74.0	17.8	2.09	11.71	63.5	54.48	57.48	220/90
		11/21/21	Normal	61	11.30	8.27	90.8	66.5	24.3	3.03	12.44	67.2	47.15	52.96	180/95
		12/5/21	Normal	71	10.24	4.00	81.7	31.9	49.8	6.24	12.54	56.5	43.32	45.61	208/98
		12/19/21	Normal	71	11.54	9.83	100.0*	94.5	5.5	1.66	10.46	64.8	60.69	61.76	180/90
		2/7/22	Normal	82	10.51	9.03	87.7	75.3	12.4	1.48	11.99				
2 (0)	Chronic myocarditis, slight myocardial insufficiency, auricular fibrillation	11/9/21	Aur Fibr	110	19.94	16.10	96.8	78.2	18.6	3.84	20.59	111.3	31.37	37.69	93 mm
		11/12/21	Normal	126	16.24	14.48	95.1	84.2	10.9	1.76	17.08	92.3	37.25	43.86	120/85
		12/16/21	Aur Fibr	124	17.38	9.46	99.0	53.9	45.1	7.92	17.56	94.9	41.24	47.63	
		1/13/22	Aur Fibr	125	21.01	10.81	92.7	47.7	45.0	10.20	22.67	122.5	50.50	59.20	
		2/3/22	Aur Fibr	130	22.72	12.01	98.1	51.9	46.2	10.71	23.15	125.1	51.29	64.86	
		2/28/22	Aur Fibr	126	22.46	11.13	97.1	48.1	49.0	11.33	23.13	125.0	47.41	62.91	95 mm
		3/1/22	Normal	128	19.60	14.86	92.5	70.1	22.4	4.74	21.19	114.5	52.23	60.80	125/90
		3/4/22	Normal												
		3/24/22	Aur Fibr	132	21.13	13.05	96.0	63.1	36.6	8.08	20.91	113.0	53.18		135/85
		3/31/22	Normal	127	21.23	12.18	100.0†	77.9†	42.1	9.07	21.03	113.7	51.43		110/70
		4/6/22	Normal	130		16.02		68.4			23.42	126.6			
3 (3)	Arteriosclerosis, emphysema, myocardial degeneration, auricular fibrillation	12/1/21	Aur Fibr	52	16.08	12.32	98.4	75.4	23.0	3.76	16.35	89.5	50.65	56.44	118 mm
		12/6/21	Normal	61	16.80	16.48	94.4	92.6	1.8	0.32	17.79	96.2	39.56	42.22	130/80
		12/8/21	Normal	63	15.74	13.65	100.0*	91.9	8.1	2.09	14.85	80.3	41.88	42.33	135/70
		12/14/21	Normal	64	15.60	14.45	100.0*	96.2	3.8	1.14	14.91	80.6	37.70	38.85	130/80
		12/21/21	Normal	58	13.60	13.28	95.9	93.6	2.3	0.32	14.18	76.7	42.99	43.34	140/80
		1/6/22	Normal	63	12.89	12.73	93.4	92.3	2.3	0.16	13.80	74.9	39.94	41.19	
		1/20/22	Normal	68	15.58	14.09	100.0†	91.3	8.7	1.34	15.43	83.4	52.12	53.08	140/80
		2/14/22	Normal	61	17.65	16.14	93.8	85.9	7.9	1.51	18.81	101.7	52.48	53.14	160/90
		3/2/22	Normal	56	16.84	13.63	92.1	74.6	17.5	2.21	18.25	98.8	54.37	56.34	140/85
		3/30/22	Normal	63	16.27		97.7				16.65	90.0	54.49		150/85
		3/31/22	Normal			15.82		87.8			18.02	97.4		59.02	

No.	Diagnosis	Date	Aur. Fib	50	9.05	3.50	100.0*	46.0	51.0	5.15	8.47	45.7	43.11	49.08	92 mm
1 (5)	Chronic rheumatic endocarditis, mitral stenosis and insufficiency, auricular fibrillation	12/20/21	Normal	50	9.05	3.50	100.0*	46.0	51.0	5.15	8.47	45.7	43.11	49.08	92 mm
		1/4/22	Normal	87	8.19	3.78	92.8	42.8	50.0	4.41	8.83	47.7	43.90	46.35	120/70
		2/1/22	Normal	87	10.62	4.71	98.1	43.5	51.6	5.91	10.83	58.5	55.20	58.62	140/80
		3/25/22	Normal	82	10.96	7.22	91.5	68.2	32.3	3.71	11.60	62.7	49.89	52.83	120/75
5 (10)	Arteriosclerosis, emphysema, myocardial insufficiency, auricular fibrillation	3/25/22	Normal	89	12.18	7.78	96.9	61.9	35.0	4.10	12.57	67.9	54.36	59.84	120/70
		1/13/21	Aur. Fib		15.64	4.88	91.6	29.5	65.1	10.76	16.54	89.4	53.67	62.34	182 mm
		1/31/22	Normal		15.50	15.15	90.4	88.4	2.0	0.35	17.14	92.7	56.25	57.26	130/86
		2/6/22	Normal		15.91	14.72	90.1	83.5	6.7	1.10	17.65	95.4	55.71	59.83	
6 (7)	Exophthalmic goiter, cardiac hypertrophy and dilatation, myocardial insufficiency, auricular fibrillation	2/9/22	Normal		14.32	12.93	88.3	79.8	8.5	1.39	16.21	87.6	54.32	57.14	
		2/3/22	Aur. Fib	38	17.85	9.38	93.6	49.2	44.4	8.47	19.07	103.1	51.49	60.75	88 mm
		2/11/22	Normal	44	17.46	11.60	91.7	60.9	30.8	5.86	19.04	102.9	60.37	61.91	144/92
		2/21/22	Normal	60	18.52	7.8	100.0†	39.4§	60.6	11.24	18.43	99.6	59.32	68.55	130/60
7 (8)	Arteriosclerosis, chronic pulmonary emphysema, cardiac hypertrophy, myocardial insufficiency, auricular fibrillation	2/24/22	Normal		15.16	15.16		85.8			18.02	97.4	58.78	58.78	
		3/8/22	Normal		9.57	9.57		65.1			14.70	79.5	58.85	58.85	
		3/27/22	Normal	64	14.68	10.18	97.1	67.1	30.0	4.58	15.02	81.1	53.25	61.63	135/60
		4/13/22	Aur. Fib	48	19.66	14.94	91.5	69.6	22.0	4.72	21.48	116.1	62.20	60.10	100 mm
8 (4)	Chronic rheumatic endocarditis, mitral stenosis and insufficiency, auricular fibrillation	4/18/22	Normal	63	17.22	16.34	89.9	85.3	4.6	0.88	19.16	103.6	62.85	63.43	110/55
		4/23/22	Normal	67	17.67		91.7				19.27	104.2	63.06		
		12/15/21	Aur. Fib	36	17.81	15.13	94.3	80.1	14.2	2.68	18.89	102.1	38.36	38.82	80 mm
		1/16/22	Normal	46	17.70	14.52	89.5	73.4	16.1	3.18	19.78	106.9	47.75	49.07	135/85
9 (12)	Chronic rheumatic endocarditis, mitral stenosis and insufficiency, slight emphysema, auricular fibrillation	3/1/22	Normal	42	14.02	14.02		69.1			20.30	109.7	55.40	55.40	120/78
		3/22/22	Normal	47	19.72	15.10	96.8	74.1	22.7	5.62	20.38	110.2	55.44	61.14	
		1/6/22	Aur. Fib	40	14.04	8.65	93.7	57.8	35.9	5.34	14.98	81.0	39.92	45.92	102 mm
		1/16/22	Normal	33	15.80	9.13	92.4	53.4	39.0	3.18	17.10	92.4	54.15	59.27	145/75
		1/30/22	Aur. Fib	49	20.32	10.30	100.0*	52.7	17.3	10.02	19.55	105.4	56.52	68.08	92 mm
		2/10/22	Aur. Fib	68	18.88	10.37	95.1	32.2	42.9	8.51	19.86	107.4	53.75	63.74	

\* Difference between arterial oxygen content and oxygen capacity is probably due to excess oxygen in physical solution Oxygen capacities checked by saturating a second sample of blood

† Difference between arterial oxygen content and oxygen capacity is within experimental error

‡ Patient held arm stiff and made a fist, causing venous stasis

§ Patient near an open window, cold and cyanotic

TABLE 2—CASES IN GROUP I

Case No	Date	Pulse		Respiration		Artery Used	Digitals	Quinidin Sulphate	Remarks
		Arterial Puncture	Venous Puncture	Arterial Puncture	Venous Puncture				
1 (2)	11/7/21	70	70	28	28	Left radial	6 cc tincture	10.5 gm	A few rales at bases, no edema Marked subjective improvement
	11/8/21	60	60	22	22	Right radial			
	11/21/21	66	58	24	24	Right radial			
	12/5/21	58	60	22	24	Right radial			
	12/10/21	52	60	18	20	Right radial	0	9.7 gm	Increasing cardiac reserve Continued improvement L-asitide NO signs cardiac failure No subjective improvement
	2/7/21	60	60	14	14	Right brachial			
	11/9/21	61	68	16	16	Right brachial			
	11/12/21	78	76	14	14	Right brachial			
	12/16/21	60	70	20	16	Right brachial	0	Started again	Dyspnea after walking Weakness No signs cardiac failure No subjective improvement
	1/13/22	58	61	18	20	Right brachial			
	2/3/22	58	63	14	16	Right brachial			
	2/28/22	61	62	12	14	Right brachial			
2 (4)	3/1/22	72	76	14	12	Left brachial	0	15.6 gm 0.1 gm Q D	Feels very tired and nervous Asked to discontinue quinidin No signs cardiac failure Marked subjective improvement
	3/1/22	72	72	14	20	Left brachial			
	3/21/22	64	66	16	16	Left brachial			
	3/31/22	64	72	16	11	Left brachial			
	4/6/22	54	54	14	14	Left brachial	0	11.0 gm	Feels stronger Cardiac reserve increased
	12/1/21	60	66	24	26	Right radial			
	12/6/21	101	110	18	20	Right radial			
	12/8/21	66	58	20	22	Right radial			
	12/14/21	76	80	22	24	Right radial			
	12/21/21	66	64	20	22	Right radial	0	13.0 gm	Marked subjective improvement Some dyspnea and precordial pain Greatly increased cardiac reserve
	1/6/22	62	66	18	20	Right radial			
	1/20/22	62	58	16	20	Right radial			
	2/11/22	60	56	16	16	Brachial			
3 (5)	3/2/22	60	60	24	16	Right radial	0	10.8 gm	Cyanosis No edema, no rales Great subjective improvement No cyanosis
	3/30/22	60	60	16	16	Right radial			
	3/31/22	60	60	16	16	Right radial			
	12/20/21	72	66	20	16	Left brachial			
	1/4/22	76	70	20	11	Left brachial	0	23.4 gm	Increased cardiac reserve Rales at bases, cyanosis, dyspnea and edema Subjective improvement Few rales No dyspnea Patient near open window Chilly and cyanotic
	2/1/22	80	72	22	22	Left brachial			
	2/18/22	90	72	24	22	Left brachial			
	3/23/22	60	60	20	22	Left brachial			
	1/13/22	52	64	24	20	Right brachial	2.7 gm leives	10.8 gm	No signs cardiac failure Increased cardiac reserve Peculiar dusky cyanosis No other signs cardiac failure
	1/31/22	100	100	22	22	Left brachial			
	2/6/22	72	85	22	22	Left brachial			
	2/9/22	100	100	28	30	Left brachial			
4 (7)	2/9/22	100	71	24	22	Left brachial	28 cc tincture	11.7 gm	Only a slight tinge of cyanosis Increased cardiac reserve
	2/11/22	80	80	26	26	Left brachial			
	2/21/22	76	72	28	21	Left brachial			
	2/24/22	76	72	28	20	Left brachial			
	3/8/22	76	76	22	21	Right radial	0	16.0 gm	No signs cardiac failure Low cardiac reserve Marked subjective improvement
	3/27/22	78	80	22	20	Right radial			
	4/13/22	56	48	18	16	Right radial			
	1/18/22	48	46	18	20	Right radial			
	1/23/22	120	110	24	20	Right radial	18 cc tincture	17.1 gm	Cardiac reserve increasing Rales at bases, cyanosis, liver enlarged Slight cyanosis, few rales, no subjective improve ment 11.4 gm after
	12/15/21	105	120	24	21	Right radial			
	1/16/22	105	104	26	24	Brachial			
	3/1/22	90	86	26	21	Brachial			
5 (12)	3/2/22	88	72	28	28	Right brachial	22 cc tincture	2.0 gm more	No cyanosis, no rales
	1/6/22	60	60	18	20	Brachial			
	1/16/22	64	60	20	21	Brachial			
	1/30/22	80	70	18	18	Brachial			
	2/10/22								

increase may have been either a physiologic response to a demand for more hemoglobin or the result of iron therapy. The patient's vital capacity improved.

CASE 4 (5) (Tables 1 and 2)—Patient, a female, white, aged 38 years, was admitted, Dec 19, 1921, and discharged Dec 31, 1921, improved and with normal mechanism.

*History*—She had had rheumatism at 8 years. Her present illness began in May, 1920, with dyspnea on slight exertion. She was a dispensary patient from June to September 1920. There were only occasional symptoms of cardiac failure during the period from September, 1920, to November, 1921, when there was a rather rapid decrease in cardiac reserve as shown by marked dyspnea, edema of the ankles and palpitation. The patient received digitalis in the dispensary.

*Examination*—There were no signs of congestive heart failure. The heart was slightly enlarged to the left. A systolic thrill was noted at the apex. The rhythm was totally irregular. At the apex there was a short, high pitched, systolic murmur, and a low pitched rumbling murmur in mid-diastole. The liver was not felt.

*Diagnosis*—Chronic rheumatic endocarditis, mitral stenosis and insufficiency, myocardial insufficiency, auricular fibrillation.

*Treatment*—Digitalis was not necessary. December 22, the use of quinidin was begun, and on December 26 the patient reverted to normal mechanism which was present on discharge and was still present when the patient was seen in April, 1922.

This patient showed evidence of marked structural cardiac change with rapidly diminishing cardiac reserve. With return to the normal mechanism, there was a great improvement subjectively and the cardiac reserve improved tremendously, so that the patient is now able to do all her own housework, without dyspnea, edema or palpitation. With the onset of the normal rhythm the arterial saturation was decreased, but the following analysis showed that it had returned to normal. There was an actual decrease in the venous oxygen saturation with the onset of the normal mechanism, but since the arterial saturation was decreased to a greater extent, the coefficient of utilization was diminished, showing an improvement in the circulation. The gaseous exchange of the blood thus took place on a lower level during the normal mechanism than during fibrillation. The cause for the venous anoxemia during the normal mechanism may have been the rather severe anemia which the patient had, for with the improvement of the anemia the venous saturation improved almost to the normal figure. The oxygen consumption was decreased. The vital capacity showed marked improvement.

CASE 5 (10) (Tables 1 and 2)—Patient, female, white, aged 73 years, was admitted, Jan 11, 1922, and discharged, Feb 13, 1922, improved and with normal mechanism.

*History*—Symptoms began one year ago with dyspnea on exertion. Slight cough has been present since this time with occasionally some edema of the



ankles. She came to the dispensary in June, 1921, and was kept on digitalis from that time. September 10, an electrocardiogram showed auricular fibrillation. In the last month the dyspnea became worse.

*Examination*—Patient was senile, she had slight dyspnea, but no cyanosis. There were signs of fairly marked emphysema, with congestion of the bases of the lungs. The heart was enlarged. The rhythm was totally irregular. Loud systolic murmur was heard over the base, and was well transmitted to the neck. The pulse was slow with a small deficit. The peripheral arteries were not thickened. There was no edema.

*Diagnosis*—Arteriosclerosis, emphysema, myocardial insufficiency, auricular fibrillation.

*Treatment*—Digitalis was not necessary. January 28, quinidin sulphate was begun, and January 30 the normal mechanism was restored. Late on January 31 fibrillation was present, reverting to the normal mechanism again February 3. Late on February 6 fibrillation began again, and February 8 normal mechanism was again restored. Normal rhythm was present on discharge.

This was a senile patient who had probably been fibrillating for one year, during which time her cardiac reserve gradually declined. She was improved clinically by the reversion to the normal mechanism. It is interesting to note the presence of an unusually high average systolic blood pressure (182 mm mercury) during fibrillation. During the normal mechanism the blood pressure fell to 130 systolic and 86 diastolic. There was a decrease in the arterial saturation with the normal rhythm, which did not return to normal later, probably because of the high grade of emphysema. During fibrillation the blood flow may have been so slow that the blood remained in the lung capillaries long enough to become fully oxygenated in spite of the emphysema, but with the normal mechanism and the improved circulation rate this was not possible. The circulation was improved by the normal mechanism, as is shown by the greatly improved venous saturation and the diminished coefficient of utilization. The oxygen consumption was decreased and the oxygen capacity slightly increased.

The patient was again admitted to the hospital early in March, 1922, and was found to be fibrillating. No attempt was made to give quinidin on this admission, and the patient died of a cerebral accident a few days later.

**CASE 6 (7)** (Tables 1 and 2)—Patient a male, white, aged 58 years, was admitted Feb. 3, 1922, and discharged March 11, 1922, improved and with normal mechanism.

*History*—Nervousness began in October, 1914. March 6, 1915, ligation of the right inferior thyroid artery was done. March 25, 1915, ligation of both superior thyroid arteries was done. May 5, 1915, an injection of boiling water was made into both lobes of the thyroid. June 1, 1915, a left lobectomy was made. The patient improved after operation. Jan. 24, 1916, a right lobectomy with partial excision of isthmus of the thyroid was made. The patient improved. Eighteen months after the last operation, the patient noticed a lump on the right side of his neck. He later became dyspneic and had palpitation. Three weeks ago he began to sleep propped up in bed and his eyes became prominent.

*Examination*—He was a small, undernourished man, very nervous, with moist skin, cyanosis of lips, fingers and ear lobes. Exophthalmos was present and a small lump on the right side of the neck. Râles were heard at the lung bases posteriorly. The heart was slightly enlarged. The rhythm was totally irregular. A soft blowing systolic murmur was transmitted feebly to the axilla. The apex beat rate was 140—deficit 18. The liver was 11 cm below the costal margin. There was no edema.

*Diagnosis*—Exophthalmic goiter, cardiac hypertrophy and dilatation, myocardial insufficiency, auricular fibrillation.

*Treatment*—The patient was thoroughly digitalized, pulse rate continuing in the neighborhood of 120, with a pulse deficit of 18. February 8 the use of quinidin sulphate was begun and February 11 the patient reverted to normal mechanism. February 21 the basal metabolism was 49 per cent above normal. February 28 radium treatment was given to the thyroid. March 5 the patient reverted to fibrillation. March 7 the normal mechanism again restored. The patient was discharged with a normal rhythm. The normal mechanism was still present when the patient was seen April 29, 1922.

This was a case of marked cardiac failure and auricular fibrillation secondary to toxic goiter. There was a most striking improvement clinically with reversion to the normal mechanism. His palpitation, dyspnea, edema and râles, which did not clear up under digitalis, disappeared under the normal mechanism. There was marked distress when he reverted to fibrillation for two days. He is now able to work again. The arterial saturation decreased with the onset of the normal mechanism and later returned to normal. The increase in the venous saturation and lowered coefficient of utilization show an improved circulation. There was a gradual decrease in the oxygen capacity. The oxygen consumption was diminished. There was a steady rise in the vital capacity.

CASE 7 (8) (Tables 1 and 2)—Patient, a male, white, aged 57 years, was admitted April 5, 1922, and discharged April 23, 1922, improved and with normal mechanism.

*History*—Two years ago, dyspnea on exertion was first manifested. About eight months ago, he stopped work because of increasing dyspnea and edema.

*Examination*—He had a moderate cyanosis of his lips and finger tips, but no dyspnea. The jugulars were prominent and distended. Signs of a rather marked emphysema, and moist râles at lung bases posteriorly were noted. The heart was enlarged. A totally irregular rhythm and faint systolic murmur at the apex, not transmitted, were noted. The pulse was 64, with a deficit of a few beats. The vessels were thickened and tortuous. There was a fluid wave in the abdomen. The liver was 6 cm below the costal margin. He had edema of the feet, ankles and legs up to the groin. The Wassermann test was negative.

*Diagnosis*—Arteriosclerosis, emphysema, cardiac hypertrophy, myocardial insufficiency, auricular fibrillation.

*Treatment*—From April 5 to April 13 digitalis was given, with disappearance of most of the edema. April 13 the use of quinidin sulphate was begun and April 16 the patient reverted to normal mechanism which was present on discharge.

This patient, with a "large lung" emphysema with auricular fibrillation, came into the hospital with a marked degree of heart failure, and under digitalis most of the edema disappeared. He showed marked improvement clinically with the onset of the normal rhythm and his cardiac reserve increased. There was a decrease in the arterial saturation which later increased again, although the normal limit was not reached, probably because of the marked emphysema. The venous saturation increased, the coefficient of utilization, the oxygen consumption and the oxygen capacity decreased. There was no change in the carbon dioxide content of the arterial or venous blood. It is interesting to note the high carbon dioxide content and capacity (78.21 volumes per cent) of the venous plasma. Scott<sup>16</sup> has called attention to the high carbon dioxide capacity of the plasma in chronic pulmonary emphysema but has shown that there was no appreciable change in the  $p_H$  of the blood. Respiratory experiments carried out on this patient showed a high alveolar carbon dioxide and there was an improvement in the respiratory minute volume with the normal mechanism.

CASE 8 (4) (Tables 1 and 2) —Patient, female, white, aged 48 years, was admitted Dec 12, 1921, and discharged Dec 31, 1921, improved and with normal mechanism.

*History* —Patient had an acute attack of rheumatic fever fourteen years ago, four years later she had a second attack with cardiac involvement. There was dyspnea on exertion, but she lived quietly and within her cardiac reserve, until January, 1921, when she overworked. In March, 1921, her heart began to beat rapidly and there was marked orthopnea. She was in bed for one month and took digitalis. Since then she has been in bed at intervals.

*Examination* —There was slight cyanosis of lips, but no dyspnea. The heart was not enlarged. No thrill was present. Rhythm was totally irregular. A short systolic murmur and a short early diastolic murmur were heard at the apex. A few râles were heard at the bases of the lungs. Edema was absent. The Wassermann test was negative.

*Diagnosis* —Chronic rheumatic endocarditis, mitral stenosis and insufficiency, myocardial insufficiency, auricular fibrillation.

*Treatment* —Digitalis was not necessary. December 16 the use of quinidin sulphate was begun. It was discontinued December 19 because of nausea and abdominal pain. December 24 quinidin sulphate was used again and the patient reverted to normal mechanism. The patient was discharged with normal rhythm and it was still present in April, 1922.

This case showed an advanced structural cardiac change with almost no cardiac reserve at the time of admission. After reversion to the normal mechanism she was tremendously improved subjectively and the rhythm was still regular when she was seen in April, 1922. She was doing her own housework. After the onset of the normal mechanism, the arterial saturation decreased and later returned to normal. There was a decrease in the venous saturation and an increase in the coefficient of utilization under the normal rhythm. There was an increase in

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16 Scott, R. W. Arch. Int. Med. 26:544 (Oct.) 1921.

oxygen consumption and in oxygen capacity and an improvement in the vital capacity

CASE 9 (12) (Tables 1 and 2) —Patient, a male, white, aged 60 years was admitted Jan 5, 1922, and discharged Feb 10, 1922, improved, but with auricular fibrillation

*History*—Dyspnea and palpitation began fifteen years ago, when digitalis was given. Dyspnea has gradually increased in severity with occasional orthopnea. Edema of ankles was present for three months. A cerebral accident two and one-half years ago resulted in an aphasia of a few weeks duration. A similar cerebral accident occurred in October, 1921, which left a permanent aphasia.

*Examination*—Patient had a marked arteriosclerosis, dyspnea, marked cyanosis, chronic passive congestion of the lungs and some emphysema. The heart was enlarged, and the rhythm was totally irregular. A systolic apical murmur was transmitted to the axilla. Localized presystolic murmur was heard at the apex. The liver edge was palpable to the level of the umbilicus. There was no edema. The Wassermann test was negative.

*Diagnosis*—Chronic rheumatic endocarditis, mitral stenosis and insufficiency, myocardial insufficiency, slight emphysema, auricular fibrillation.

*Treatment*—From January 6 to 11 digitalis was given, bringing the cardiac rate to 65 with a pulse deficit of from 6 to 10 beats. January 12 the use of quinidin sulphate was begun, and on January 14 normal mechanism was restored. January 21 there was reversion to fibrillation and January 23 quinidin sulphate was discontinued because of rise in temperature and the presence of râles in the chest. Digitalis was then given. January 31 the use of quinidin was begun again but the patient had a chill with a rise in temperature and quinidin was discontinued. February 5 digitalis was started again. The patient was discharged with fibrillation still present.

This case of auricular fibrillation with cardiac failure was digitalized before quinidin sulphate was begun. Subjectively the patient was not improved by the normal mechanism, and later when he reverted to fibrillation he could not take quinidin without an unfavorable reaction. The slight anoxic anoxemia present during the fibrillation is accounted for by the pulmonary congestion. There was a further increase in the anoxic anoxemia with the onset of the normal mechanism, but February 10, after reversion to fibrillation, when there were no signs of pulmonary congestion, the arterial saturation was 100 per cent. The venous anoxemia and the coefficient of utilization increased, indicating that there was no improvement of the blood flow with the normal mechanism. There was a progressive rise in oxygen capacity which was probably a compensatory mechanism. The oxygen consumption increased. The vital capacity decreased but later improved on reversion to fibrillation.

#### GROUP II

CASE 10 (6) (Tables 3 and 4) —Patient, a male, white, aged 58 years, was admitted Jan 3, 1922, and discharged Jan 10, 1922 improved, and with normal mechanism.

*History*—Dec 7, 1920, the patient was awakened by a "pounding of his heart" lasting two hours, followed by dyspnea, weakness and edema of ankles.

TABLE 3—BLOOD GASES IN CASES OF GROUPS II AND III

Case No	Diagnosis	Date	Mechanism	Vital Capacity, per Cent Normal	Oxygen Content		Oxygen Saturation		Coefficient of Utilization, per Cent	Oxygen Consumption, Volume per Cent	Oxygen Capacity, Volume per Cent	Hemoglobin, per Cent	Carbon Dioxide		Blood Pressure
					Arterial, Volume per Cent	Venous, Volume per Cent	Arterial, per Cent	Venous, per Cent					Arterial, Volume per Cent	Venous, Volume per Cent	
10 (6)	Chronic rheumatic endocarditis, mitral stenosis and insufficiency, cardiac hypertrophy and dilatation, slight myocardial insufficiency, auricular fibrillation	1/5/22 1/10/22 1/17/22 2/2/22 2/23/22	Normal Normal Normal Normal Normal	67 92 90 92 92	11.60 15.15 16.95 15.96 14.74	4.85 7.46 11.92 12.81 11.87	86.2 100.0* 100.0* 95.6 93.5	36.8 50.1 83.4 76.8 75.3	49.4 49.9 16.6 18.9 18.2	6.75 7.69 5.03 3.15 2.87	13.46 14.88 14.03 16.60 15.76	72.8 80.4 77.3 90.2 85.2	36.84 45.54 47.15 51.83 51.30	41.03 50.30 50.52 56.83 56.61	110/80 120/75 130/80 130/80 130/80
11 (1)	Arteriosclerosis, myocardial degeneration myocardial insufficiency, auricular fibrillation	1/12/22 4/1/22	Normal Normal	83 90	17.53 19.96	10.78 12.63	90.5 96.4	55.5 61.0	35.0 35.4	6.80 7.33	19.42 20.70	105.0 111.9	49.60 56.87	56.77 64.00	160/110 160/105
12 (17)	Chronic rheumatic endocarditis, mitral stenosis and insufficiency, myocardial insufficiency, auricular fibrillation	11/30/21 12/13/21	Aur Fibr Aur Fibr	2300 c.c. 1,400 c.c.	17.42 18.10	7.31 2.94	88.0 97.6	66.9 15.8	51.1 81.8	10.11 15.16	19.79 18.54	107.0 100.2	48.19 36.06	53.66 46.36	106 mm
13 (16)	Chronic rheumatic endocarditis, mitral stenosis and insufficiency, myocardial insufficiency, auricular fibrillation	12/22/21	Aur Fibr	2800 c.c.	21.23	16.91	94.0	74.8	19.2	4.32	22.58	122.1	39.00	45.00	120 mm
14 (14)	Chronic rheumatic endocarditis, mitral stenosis and insufficiency, myocardial insufficiency, auricular fibrillation	3/8/22	Aur Fibr	48	21.36	16.40	98.1	75.3	22.8	4.96	21.78	117.7	48.73	57.79	120 mm
15 (17)	Chronic rheumatic endocarditis, mitral stenosis and insufficiency, auricular fibrillation	11/11/21 11/18/21	Aur Fibr Aur Fibr	47 37		4.35 1.77† 7.35		26.6 9.6 40.0			16.38 18.30	88.54 99.40		35.34 56.10† 53.76	95 mm 130 mm

\* Difference between oxygen content and oxygen capacity is probably due to excess oxygen in physical solution. These were checked by saturating a second sample of blood.

† Deep vein punctured in attempt to get arterial blood. Recorded as of interest, showing difference in saturation between blood from a very deep vein at the elbow and the superficial vein at bend of elbow.

TABLE 4—CASES IN GROUPS II AND III

Case No	Date	Pulse		Respiration		Artery Used	Digitals	Quinidin Sulphate	Remarks
		Arterial Puncture	Venous Puncture	Arterial Puncture	Venous Puncture				
10 (6)	1/5/22 1/10/22 1/17/22 2/2/22 2/23/22	76 66 76 78 74	80 68 72 72 74	18 21 18 16 22	22 21 19 18 22	Brachial Brachial Radial Brachial Right brachial	0	5.4 gm	Slight cyanosis No cyanosis Subjective improvement
11 (1)	1/12/22 4/1/22	56 60	54 68	20 20	18 18	Brachial Brachial	8-22 to 9-10, 47 c c 9-23 to 10-8, 96 c c	9-20 to 9-23, 16 gm 5.4 gm	No signs cardiac failure    Cardiac reserve good
12 (15)	11/30/21 12/13/21	66 62	72 60	26 16	24 18	Brachial Brachial	48 c c	160 gm in two attempts	Cyanosis    No rales    No edema Few rales at both bases
13 (16)	12/22/21	48	52	24	28	Brachial	52 c c in two courses 12 c c	316 gm in two trials 6.2 gm	Cyanosis of lips    Rales at bases No cyanosis
14 (14)	3/8/22	64	66	20	22	Right radial	+	0	Cyanosis, rales    No edema Dyspnea
15 (17)	11/11/21		98 56		28 21				

He was in the hospital for three weeks and was found to have fibrillation. He was treated with digitalis. He was discharged without signs of failure. In February, 1921, he had a second attack of cardiac failure and was in the hospital for four weeks, following which he was kept on digitalis.

*Examination*—There were no signs of cardiac failure, except a slight cyanosis. The heart was slightly enlarged. The rhythm was totally irregular. A loud blowing systolic murmur was heard at the apex, and a systolic murmur over the pulmonic area. This murmur was transmitted to the neck vessels.

*Diagnosis*—Chronic rheumatic endocarditis, mitral stenosis, mitral insufficiency, cardiac hypertrophy and dilatation, slight myocardial insufficiency, auricular fibrillation.

*Treatment*—Digitalis was not necessary. January 3 the use of quinidin sulphate was begun and the patient reverted to normal mechanism. January 4 He was discharged with normal mechanism. Patient still had a normal rhythm when seen in March, 1922.

This patient had two very severe cardiac breaks, and had very little cardiac reserve, but with the continuance of the normal mechanism this was greatly improved. Unfortunately, no blood studies were made during the period of fibrillation. After the onset of the normal mechanism the arterial saturation was low, later going up to a normal level where it remained. There was a venous anoxemia at first but subsequent examinations after the continuance of the normal mechanism showed a great improvement both in the venous saturation and in the coefficient of utilization. The patient's anemia improved and there was marked increase in the vital capacity.

CASE 11 (1) (Tables 3 and 4)—Patient, a male, white, aged 49 years, was admitted Aug 23, 1921, and discharged Oct 29, 1921, improved, and with normal mechanism.

*History*—Precordial pain began in April, 1921. Later, there was dyspnea on exertion and the patient went to a hospital for six weeks. Soon after discharge he began to have abdominal pain and edema of the ankles. When he was admitted here he was complaining of shortness of breath, pain in the stomach and swelling of the feet.

*Examination*—He had some dyspnea, râles at bases of the lungs and edema. The cardiac rhythm was totally irregular. The heart was enlarged but there were no murmurs. The liver was enlarged. The Wassermann test was negative. The apex rate was 120, with a pulse deficit of 10. The peripheral arteries were tortuous and thickened.

*Diagnosis*—Arteriosclerosis, myocardial degeneration, myocardial insufficiency, auricular fibrillation.

*Treatment*—From August 23 to Oct 8, 1921, the patient received digitalis, but showed only moderate improvement. October 8 the use of quinidin sulphate was begun and the patient reverted to normal mechanism. October 10 He was discharged with a normal mechanism.

The patient showed marked myocardial change with a very slight cardiac reserve. Digitalis cleared up his signs of cardiac failure, but as soon as the patient got up the signs returned. With the normal mechanism there was a great subjective improvement, and the building up of the patient's cardiac reserve was very rapid. He was able to

start moderate work again without discomfort. The normal mechanism has persisted for eight months. The blood gas studies were not in progress when the patient reverted to the normal mechanism but subsequent examinations showed, first, an arterial anoxemia which later disappeared and an increased venous saturation, without any change in the coefficient of utilization because of the rise in arterial saturation. The vital capacity increased progressively.

#### GROUP III

CASE 12 (15) (Tables 3 and 4)—Patient, male, white, aged 45 years, was admitted Nov 28, 1921, and discharged Dec 21, 1921, improved, but with auricular fibrillation.

*History*—The patient first had dyspnea eighteen years ago. The pulse was irregular in June, 1913. The first cardiac failure was in November, 1920, during an attack of bronchopneumonia. He had two subsequent attacks of cardiac failure. He has taken digitalis since April, 1921.

*Examination*—There was slight dyspnea, but no edema, no râles, and no pulse deficit. The rate was 88. The heart was not enlarged. The rhythm was totally irregular. There was a rumbling murmur throughout diastole ending a little before the first sound. The Wassermann test was negative.

*Diagnosis*—Chronic rheumatic endocarditis, mitral stenosis and insufficiency, myocardial insufficiency, auricular fibrillation.

*Treatment*—Digitalis was not necessary. December 3 the use of quinidin sulphate was started, and was discontinued December 10 because of subjective discomfort. Quinidin was given December 11 but again discontinued because of signs of cardiac failure. December 12 the use of digitalis was started again. The patient was discharged with auricular fibrillation.

The patient showed marked structural change in the heart with greatly diminished cardiac reserve. Attempts to restore the normal mechanism with quinidin sulphate failed and signs of cardiac failure appeared rapidly when digitalis was stopped. The arterial saturation was normal in spite of the pulmonary congestion. There was a marked venous anoxemia, and a high coefficient of utilization, pointing to a very sluggish circulation. This may have accounted for the high arterial saturation, because with the slow blood flow the blood had time to become fully oxygenated in the lung capillaries. The patient was finally discharged with auricular fibrillation, fairly well compensated but with a low cardiac reserve.

CASE 13 (16) (Tables 3 and 4)—Patient, a male, white, aged 39 years, was admitted Dec 21, 1921, and discharged Jan 26, 1922, improved, but with auricular fibrillation.

*History*—In August, 1919, the patient became dizzy, fainted and vomited. After this he had frequent attacks of indigestion. Dyspnea has gradually come on since then and is the chief complaint at the present time. Patient is now orthopneic.

*Examination*—There was dyspnea, slight cyanosis of the lips and fingers, râles at the bases of the lungs posteriorly. The rhythm was totally irregular, with a short systolic murmur at the apex. The second sound was followed after an interval by a soft blowing diminuendo murmur. There was no pulse deficit.



*Diagnosis*—Chronic rheumatic endocarditis, mitral stenosis and insufficiency, myocardial insufficiency, auricular fibrillation

*Treatment*—Digitalis was not necessary December 23 the use of quinidin sulphate was started but discontinued December 30 because of diarrhea From Jan 1 to 8, 1922, digitalis was given January 9 quinidin sulphate was given again January 19 quinidin was discontinued because of the return of cardiac failure and digitalis was given again The patient was discharged fibrillating

This patient was admitted with a mild degree of heart failure but with very little cardiac reserve Two trials were made with quinidin sulphate without changing the rhythm As soon as digitalis was stopped, signs of cardiac failure developed at once Arterial and venous samples taken once during fibrillation showed a very slight anoxic anoxemia with a normal venous saturation and a normal coefficient of utilization

CASE 14 (Tables 3 and 4)—Patient a female, white aged 22 years, was admitted March 3, 1922, and died March 12, 1922

*History*—She had had repeated attacks of tonsillitis The tonsils were excised An attack of rheumatic fever and the first cardiac break came in 1911 Two subsequent attacks of cardiac failure, with discovery of fibrillation, occurred in June, 1920 She has been fairly comfortable with the use of digitalis since the last attack but becomes very dyspneic and has palpitation on exertion

*Examination*—The heart was enlarged At the apex there was a blowing systolic murmur, and rumbling middiastolic murmur The rhythm was totally irregular The apex rate was 92 the radial pulse was 84 There were no rales and no cyanosis, but there was a slight edema of the ankles The Wassermann test negative

*Diagnosis*—Chronic rheumatic endocarditis, mitral stenosis and insufficiency, cardiac hypertrophy and dilatation, myocardial insufficiency, auricular fibrillation

*Treatment*—From March 3 to 8, 1922, digitalis was given March 6, the use of quinidin sulphate was begun and patient reverted to normal mechanism March 11 During the day she was comfortable, at 7 30 p m, she complained of palpitation and orthopnea The apex rate was 120, the radial pulse was 60, a typical two to one rhythm At 2 a m, March 12, the patient had a short convulsion and died A necropsy was not permitted but it was supposed that she had cerebral embolism This was the only fatality directly attributable to the use of quinidin in the series reported in this paper

This patient showed marked structural cardiac changes with a great functional impairment of the heart The circulation was quite efficient when the patient was at rest, as shown by the normal arterial and venous saturation The coefficient of utilization was normal The vital capacity, however, was greatly diminished The patient died shortly after the onset of the normal mechanism so that studies were not made on the blood gases after reversion to the normal rhythm

CASE 15 (17) (Tables 3 and 4)—Patient, female, colored, aged 22 years, was admitted Nov 9, 1921 and died Nov 28 1921

*History*—She had had rheumatic fever at 11 years, "dropsy" at 15 years, during a cardiac failure lasting ten months An attack of influenza in 1918 was followed by cardiac failure She had pneumonia in March, 1921, which was

followed by the present attack of cardiac failure. Edema and dyspnea, which had occurred only during the menses, now became permanent. She had occasional orthopnea.

*Examination*—There were râles at the bases of the lungs. The heart was greatly enlarged. The rhythm was totally irregular. At times a thrill, apparently systolic, was felt in the anterior axillary line in the fifth and sixth interspaces. There was a systolic thrill in the second interspace, in the region of the conus, with systolic and diastolic murmurs at the apex, and a systolic murmur in the second interspace to the left of the sternal line, with marked accentuation of the first and second sounds. The liver was almost down to the umbilicus. It was tender and pulsating. Edema of ankles was present. The Wassermann test was negative.

*Diagnosis*—Chronic endocarditis, pericarditis, mitral stenosis and insufficiency, myocardial insufficiency, auricular fibrillation.

*Treatment*—From November 11 to 18 the patient received digitalis, when it was discontinued because of nausea and vomiting. November 23 the use of digitalis was started again. The patient steadily grew worse and died.

This is a case of rheumatic heart disease with extreme structural change in the heart, and functionally marked limitation of cardiac reserve. The peripheral circulation was sluggish, as shown by the marked stagnant anoxemia. A deep vein was punctured November 18 in an attempt to do an arterial puncture. The blood taken from this vein was much less saturated than that taken from the median basilic vein. No further attempt was made to do an arterial puncture because of the patient's condition. There was an increase in oxygen capacity between the two punctures pointing to a failing circulation with an attempt to overcome the failure by an increase in hemoglobin.

#### DISCUSSION

In seven out of the nine cases studied during fibrillation and during the normal mechanism there was an increase in the venous oxygen saturation and a decrease in the coefficient of utilization under the normal mechanism. The term coefficient of utilization of oxygen carrying power of the blood was introduced by Krogh and Linhard<sup>17</sup> and was emphasized by Means and Newburgh<sup>18</sup>. This term is applied to the difference between the arterial and venous oxygen saturation in terms of percentages. It is normally below 30 per cent, with an average arterial saturation of 95 per cent and a venous saturation of 65 per cent or more. It may be pointed out that with an arterial saturation of 85 per cent and a venous saturation of 55 per cent the coefficient of utilization remains 30 per cent, and from the point of view of the systemic blood flow the circulation is just as efficient as in the first case, the respiratory exchange of the blood taking place on a lower level. Cyanosis occurs at a higher figure of oxygen saturation when an anoxic anoxemia is present as well as a stagnant anoxemia,

17 Krogh, A, and Linhard, J. Skand Arch f Physiol **27** 100, 1912.

18 Means, J. H., and Newburgh, L. H. Tr Assn Am Phys **30** 51, 1915.

than it does in the presence of a normal arterial saturation. Lunds-gaard<sup>19</sup> suggested this by indirect figures, and Stadie<sup>6</sup> by taking arterial samples proved it to be the case in pneumonia.

The improvement in the venous saturation and the decrease in the coefficient of utilization we have interpreted as due to an improvement in the systemic blood flow, if the circulation rate is increased the blood does not remain in the capillaries as long and the blood entering the veins has not given up as much oxygen to the tissues as is the case at a slower rate. If, in response to the need of the tissues, a definite volume of oxygen leaves a unit volume of blood in a given time, when twice the volume of blood passes through the same area and the same amount of oxygen is extracted, each unit volume of blood will give up only one half the volume of oxygen previously lost, and the venous oxygen saturation will, therefore, be so much the higher. The ability of the tissues to use oxygen at a very low tension is seen in anemia where the blood leaving the capillaries may be almost completely deprived of oxygen.<sup>19</sup> Meakins<sup>20</sup> showed that when an area is exposed to cold, venous blood may contain little or no oxygen. It hardly seems possible that a change in tissue metabolism, or in the cross section of the capillary bed would so constantly take place with the onset of the normal mechanism as to give the increased venous saturation, and it seems much more likely that the change is due to an improved blood flow.

All the cases, except Case 1, showed a decrease in the percentage of arterial saturation immediately after the onset of the normal mechanism. The arterial saturation returned to normal in all cases except two in which there was a pathologic lesion (emphysema) which would tend to prevent it. In Case 7, although the respiratory minute volume was increased after the onset of the normal mechanism, and the vital capacity was also increased, nevertheless, the arterial saturation was decreased immediately after the onset of the normal mechanism in spite of the improved pulmonary ventilation. We have explained this phenomenon in the following way. During fibrillation the blood flow through the lung capillaries is slow, and the blood has time to reach a maximum oxygenation. With the onset of normal mechanism and the more rapid circulation rate, the blood does not stay in the lung capillaries so long, and does not have time to reach the maximum saturation with oxygen. Later there is a compensation for this and the blood becomes fully saturated.

In seven of the nine cases in Group I there was a diminution in oxygen consumption after the onset of the normal mechanism and Case 2 showed it with each reversion to the normal rhythm. Cases

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19 Lundsgaard, C. J. *Exper. M.* 30:271, 1919.

20 Meakins, J. C. *J. Path. & Bacteriol.* 24:79, 1921.

2, 6 and 7, with high oxygen capacities, and Cases 1 and 3 with slightly lower oxygen capacities, showed a decrease in oxygen capacity after the onset of the normal mechanism or with its continuance. It would seem that the high hemoglobin content in these cases was a response to oxygen want during fibrillation, and was a compensatory mechanism. The chronic cardiac as well as the chronic pulmonary emphysema patient very often has a high oxygen capacity, which must be looked on as one of the mechanisms of the body to make up for the impaired circulation in the one case and the incomplete oxygenation of the blood in the lungs in the other, and when fibrillation is added to either condition there is an increased loss of efficiency.

Case 4 with a marked anemia improved greatly after the onset of the normal rhythm. How much of the later improvement was due to iron in the form of Blaud's pill cannot be estimated. Five other cases with moderate anemia or normal hemoglobin had an increase in the oxygen capacity with the normal mechanism.

The behavior of the carbon dioxide content of the arterial and venous blood was variable. Case 1 had a low carbon dioxide content after the onset of the normal mechanism which gradually rose to normal. Case 2 also had a low carbon dioxide content which increased with the normal rhythm and continued to increase when the patient later reverted to fibrillation. Case 3 had a carbon dioxide content at the normal level during fibrillation which decreased with the normal rhythm, later slowly rising to normal. Case 4 with a low carbon dioxide content during fibrillation had a further decrease after the normal mechanism but this later went above normal. The carbon dioxide content of the venous blood in Case 6 on one analysis was 68.55 volumes per cent at a time when the patient was near an open window, and was feeling chilly and had marked cyanosis. Case 7 showed the high carbon dioxide content which has been found in chronic pulmonary emphysema. There was no change after the onset of the normal mechanism. The carbon dioxide capacity of the venous plasma in this case was 78.21 volumes per cent.

All patients, with the exception of Case 9, showed an improvement in the vital capacity after the onset of the normal mechanism, which apparently made possible a more efficient pulmonary ventilation. The disappearance of dyspnea after the onset of the normal mechanism, coincident with improvement in the vital capacity lends weight to the suggestion of Peabody<sup>21</sup> that cardiac dyspnea is due in part to diminished vital capacity.

The details of the quinine therapy of these patients with a study of their progress from a clinical point of view are given by Burwell

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<sup>21</sup> Peabody, F. W., and Wentworth, J. A. *Arch. Int. Med.* **20**: 443 (Sept.) 1917.

and Dieuaide<sup>22</sup> in which the same case numbers are used as in the present paper. These studies show that the circulation is improved by the restoration of the normal mechanism and offer a rational basis for an attempt to bring about reversion to the normal mechanism by the use of quinidin sulphate in selected cases. The advantages of quinidin therapy seem to be four

- 1 Marked subjective improvement of the patient under the normal mechanism

- 2 Great increase in the cardiac reserve

- 3 Improved pulmonary ventilation

- 4 Improvement in the oxygen saturation of the venous blood, and on the basis of the coefficient of utilization, improvement in the peripheral systemic blood flow

#### SUMMARY

- 1 Fifteen cases of auricular fibrillation were studied from the point of view of the blood gases. Fourteen of the patients received quinidin sulphate, twelve reverted to normal mechanism. One patient died soon after reversion to normal mechanism, so that no studies were made during the normal rhythm. Unfortunately, in two other cases no studies were made in the presence of fibrillation but the progressive improvement with persistence of the normal mechanism is clearly shown. The nine remaining cases were carefully studied during fibrillation and during the normal mechanism.

- 2 Seven of the nine cases referred to above showed a definite increase in the venous oxygen saturation and a diminution in the coefficient of utilization and in oxygen consumption with the onset of normal mechanism, which was interpreted as due to an improvement in the blood flow. Two other cases showed improvement with continuance of the normal mechanism.

- 3 A reduction in percentage of the arterial oxygen saturation with the onset of normal mechanism, followed later by an increase in the percentage of arterial oxygen saturation to normal (except in two cases of emphysema), was consistently found. An explanation of this phenomenon is offered.

- 4 Two cases showed no improvement in the venous oxygen saturation nevertheless, one of these patients was greatly improved clinically while the other reverted to fibrillation almost immediately.

- 5 In three cases with a high oxygen capacity and two others with a lower oxygen capacity there was a definite fall in oxygen capacity after the onset of normal mechanism. It is suggested that the high hemoglobin present was a compensatory mechanism.

6 In one case of rather severe anemia there was a marked rise in the hemoglobin under the normal mechanism. Five other patients with moderate anemia or normal hemoglobin showed an improvement in the oxygen capacity with continuance of the normal mechanism.

7 The changes in the carbon dioxide content were variable.

8 The vital capacity was consistently increased after the onset of the normal mechanism.

# EXPERIMENTAL URANIUM NEPHRITIS

A CHEMICAL AND PATHOLOGIC STUDY \*

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It is well known that uranium nitrate given subcutaneously to laboratory animals will produce varying degrees of kidney injury. Large single doses cause an extremely acute necrosis of the cells lining the convoluted tubules, from which the animal may not recover. But when smaller doses are given over a long period of time, a marked chronic nephritis results. Dickson<sup>1</sup> demonstrated this in guinea-pigs. Christian<sup>2</sup> and his associates have produced it in rabbits. MacNider<sup>3</sup> has obtained similar results in rabbits and dogs.

The kidney pathology in experimental uranium nephritis has been described. The urinary changes during the uranium intoxication have also been followed. But since much of this work was done before the advent of blood chemistry, correlated studies of the chemical changes in the blood and urine, the renal functional tests and the pathology of the kidneys at various stages of the intoxication have not been frequently done. MacNider's researches must be excepted. He has advanced our knowledge of experimental nephritis materially.

The present work was undertaken as a correlated study of the pathology of uranium nephritis and the various chemical changes in the blood and urine. These changes were followed for long periods of time.

*Material*—A large number of rabbits were used. They varied from 9 to 12 months in age. None of them had spontaneous nephritis since their blood and urine chemistry was carefully studied before their intoxication with uranium began. Some animals were discarded because they had a spontaneous nephritis.

*Method*—Selected animals were placed in separate metabolism cages. Each was fed 100 gm. of a mixed diet of cabbage leaves, barley, carrots and alfalfa hay. They were given water ad libitum. The

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\* From the laboratories of the Santa Barbara Cottage Hospital.

1 Dickson, E. C. A Further Report on the Production of Experimental Chronic Nephritis in Animals by the Administration of Uranium Nitrate, Arch. Int. Med. **9** 557 (May) 1912.

2 Christian, H. A., and O'Hare, I. P. Glomerular Lesions in Acute Experimental Nephritis. J. Med. Research **23** 227, 1913; Christian, H. A., Smith, R. N., and Walker, I. C. Experimental Cardiorenal Disease, Arch. Int. Med. **8** 469 (Oct.) 1911.

3 MacNider, Wm. de B. A Functional and Pathologic Study of the Chronic Nephropathy Induced in the Dog by Uranium Nitrate. J. Exper. Med. **29** 513 1919. A Pathologic Study of the Naturally Acquired Chronic Nephropathy of the Dog. J. Med. Research **34** 177 1916.

urine from each cage was caught in a vessel containing 5 cc of a 5 per cent solution of hydrochloric acid to prevent the conversion of urea into ammonia ( $\text{NH}_3$ ), in the normally alkaline rabbit urine. These specimens were analyzed for albumin, and, if present, the amount in grams was recorded. Casts were searched for in centrifuged specimens.

The total nitrogen (TN) of the urine was determined by the simplified Kjeldahl method,<sup>4</sup> the urea nitrogen (UN) by the Folin and Youngberg method,<sup>5</sup> the ammonia ( $\text{NH}_3$ ) by the microchemical method of Folin and McCollum,<sup>6</sup> the creatinin (CN) by the Folin colorimetric method,<sup>7</sup> the uric acid nitrogen (UAN) by the Folin and Wu method,<sup>8</sup> and the organic acids (OA) by the Van Slyke and Palmer methods.<sup>9</sup> Acetone and diacetic acid were also sought for by the usual tests.

Sufficient blood was withdrawn from the marginal ear vein into a flask containing 10 mg of calcium oxylate to determine the nonprotein nitrogen by the method of Folin and Wu,<sup>10</sup> the urea nitrogen by the method of Folin and Wu,<sup>10</sup> the carbon dioxide by the method of Van Slyke and Cullen,<sup>11</sup> and the alkali reserve ( $Rp_H$ ) by the method of Marriott.<sup>12</sup>

From twenty-four to forty-eight hours following an initial subcutaneous injection of from 2 to 4 mg of uranium nitrate dissolved in sterile distilled water, various changes were noted in the blood and urine. The nonprotein nitrogen of the blood, for example, increased daily for from three to six days and then dropped again until approximately a normal level was reached. The animal was then allowed to rest a sufficient time to permit all acute reaction in the kidney to subside. He was then given a larger dose of uranium nitrate subcutaneously and the various tests were repeated. The rest periods between the injections of uranium varied roughly from three to sixty days. The irregularity of this interval was due to the varying time each animal

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4 Folin, O. F. A Simplified Kjeldahl Method for Urine, *J Biol Chem* **38** 461, 1919.

5 Folin, O. F., and Youngberg, G. E. Note on the Determination of Urea in Urine by Direct Nesslerization, *J Biol Chem* **38** 111, 1919.

6 Folin, O. F., and McCollum, A. B. On the Determination of  $\text{NH}_3$  in the Urine, *J Biol Chem* **2** 523, 1912.

7 Folin, O. F. Approximately Complete Analyses of Thirty Normal Urines, *Am J Physiol* **13** 45, 1905.

8 Folin, O. F., and Wu, H. A Revised Colorimetric Method for the Determination of Uric Acid in Urine, *J Biol Chem* **38** 459, 1919.

9 Van Slyke, D. D., and Palmer, W. W. Titration of Organic Acids, *Proc Soc Exper Biol & Med* **16** 140, 1919.

10 Folin, O. F., and Wu, H. A System of Blood Analysis, *J Biol Chem* **38** 81, 1919.

11 Van Slyke, D. D., and Cullen, G. E. The Bicarbonate Concentration of the Blood Plasma, Its Significance, and Its Determination as a Measure for Acidosis, *J Biol Chem* **30** 289, 1917.

12 Marriott, W. McK. A Method for the Determination of the Alkali Reserve of the Blood Plasma, *Arch Int Med* **17** 840 (June) 1916.



required to reestablish his acid base equilibrium and for his blood and urine chemistry to return as nearly to their normal levels as possible. During the later stages of the experiments, normal figures were not reached because a marked chronic nephritis had been established.

The dosage of uranium per injection was gradually increased from 2 mg. to the notably high figure of 50 mg. The longest and the shortest experiments included in this report covered periods of one hundred and seventy-five and seventy-four days, respectively. Data from animals dying during the earlier days of the experiments are not included in this study.

A statistical table was made for each animal. The various findings for each day were recorded. From these tables curves have been plotted which depict graphically the rise and fall of the chemical constituents of the blood and urine.

With all of this data before us in both table and graphic form, we have noted the various findings in each individual instance and the findings of one rabbit as compared with another. For example, we have compared the organic acids of the urine with the alkali reserve and the carbon dioxide of the blood, since each of these may be used clinically as an index of the acid-base balance. When there is an acidosis, as determined by the above methods, we have studied the ammonia of urine together with its total nitrogen and urea nitrogen. At the same time we have noted the presence and amount of albumin, of casts, of acetone and diacetic acid. Likewise we have studied the nonprotein nitrogen and urea nitrogen of the blood, noting their rise and fall and their relation to the urine findings.

Finally, these animals having given evidence of a chronic nephritis for a long period of time, their phenolsulphonephthalein elimination was determined and they were killed. A careful postmortem examination was made. The kidneys were given especially careful histologic study.

*Results*—Following an injection of uranium there occurred, within from twenty-four to forty-eight hours, a decrease in the amount of urine excreted. This was followed by a marked increase, which usually reached a maximum from the fifth to the seventh day and then gradually decreased, reaching an approximate normal from the tenth to the twelfth day.

*Urine Chemistry*—Albumin and casts appeared within twenty-four hours following the injection of uranium. They disappeared in a few days following the first and smaller injections, but during the latter part of the experiments albumin was continually present and casts were usually found for some days following each injection. There was, however, no constant relation between the amount of albumin excreted and the chemical findings of either blood or urine, nor with the degree of acidosis present. This also holds true with nephritis in man. It has frequently been demonstrated that the albumin content of the urine

DATA FROM ANIMAL I

Urea num	Day of Experi ment	Urine							Blood								
		Amount of Urine	Albu- min	Casts	Acce- tate	Dia- cetic acid	Organic Acids	Phenol sulphone phthal- ein	Total N	Urea N	NH <sub>4</sub>	Creat- inin	Uric Acid N	Non- protein N	Urea N	R <sub>pu</sub>	CO <sub>2</sub>
Normal 4 mg	0	230	0	0	0	0	90.0	88%	0.92	0.65	0	0.13	0.068	38.0	17.4	8.4	59.5
	1	80	0	0	0	0			0.43	0.30	0	0.081	0.032	39.2	18.2	8.3	51.9
	2	210	0.75	2+	0	0			1.18	0.58	0.004	0.13	0.067	48.0	26.0	7.9	37.0
	3	270	1.75	2+	0	0			0.71	0.40		0.083		69.2	43.2	8.0	44.9
	4	85	1.50	4+	0	0			0.41	0.077		0.043		100.0	64.0	8.05	42.1
	5	85	1.20	2+	0	0			0.43	0.12	0.009	0.050	0.006	133.0	88.0	8.25	52.0
	6	180	1.50	2+	Trace	0			0.68	0.50	0.0016	0.034	0.008	182.0	113.0	8.25	48.0
	7	140	0.75	0	0	0			0.53	0.24	Trace	0.042	0.008	137.0	88.0	8.2	48.9
	8	130	0.80	0	0	0			1.15	0.63	0	0.12	0.009	98.0	66.5	8.3	52.4
	9	175	0.50	0	0	0			1.37	1.19	0	0.15	0.025	50.0	33.4	8.3	49.9
4.5 mg	10	165	0	0	0	0			1.70	1.16	0	0.11	0.024	34.0	22.2	8.3	50.2
	11	140	0	0	0	0			0.73	0.53	0	0.16	0.027				
	44	190	0	0	0	0	118.4		1.94	1.83	0	0.1	0.022	66.8	42.0	8.35	51.9
	45	450	1.75	2+	0	0			2.39	1.55	0.008	0.1	0.031	103.0	67.5	8.35	55.6
	46	450	1.00	4+	0	0	114.4		1.05	0.87	0.044	0.006	0.005	105.0	90.0	8.3	59.5
8 mg	47	220	0.5	1+	0	0	120.0		1.29	1.02	0.004	0.063	0.003	152.0	122.0	8.4	63.1
	48	230	0	0	0	0	137.0		0.74	0.63	Trace	0.032	0.003	150.0	126.0	8.3	50.2
	100	340	0.5	1+	0	0	258.0		1.82	1.39	0.014	0.14	0.031	65.0	41.0	8.3	53.0
	101	155	2.0	4+	0	0	102.0		0.87	0.66	0.008	0.062	0.005	62.5	42.5	8.4	55.7
	102	220	2.0	4+	0	0	167.0		1.54	1.13	0.001	0.10	0.006	60.0	38.0	8.1	43.5
12 mg	103	250	1.0	4+	+	0	160.0		1.62	1.35	0.009	0.13	0.008	63.5	47.5	8.1	46.2
	104	500	1.0	0	0	0	330.0		2.10	1.74	0.14	0.10	0.014	68.0	42.0	8.1	43.0
	105	340	0.25	+	0	0	326.0		0.84	0.45	0.002	0.12	0.017	58.0	27.5	8.1	40.4
	108	510	0.5	1+	0	0	285.0		1.74	1.39	0.029	0.13	0.026	50.0	22.5	8.1	42.4
	109	340	0.75	2+	0	0	218.0		0.58	0.42	0.027	0.075	0.023	50.0	24.6	8.1	42.5
30 mg	110	335	0.75	2+	0	0	204.0		0.95	0.75	0.024	0.15	0.02	53.5	27.8	8.0	38.6
	111	300	0.75	2+	0	0	144.0	18%	0.69	0.50	0.02	0.09	0.027	60.0	40.0	7.8	29.4
	112																
	134	300	1.5	4+	+	+	288.0		0.84	0.41	0.026	0.075	0.02	50.0	27.0	8.1	43.8
	135	410	1.0	3+	0	0	328.0		0.86	0.48	0.03	0.066	0.018	48.0	24.5	8.1	44.6
40 mg	136	200	1.5	1+	Trace	0	208.0		0.78	0.46	0.023	0.044	0.008	52.0	25.0	8.35	55.7
	137	340	1.5	0	0	0	501.0		0.93	0.56	0.07	0.039	0.02	53.5	26.0	8.3	51.0
	138	360	1.0	0	0	0	360.0		0.91	0.62	0.042	0.05	0.018	45.0	26.5	8.1	46.2
	140																
	141																
40 mg	142	470	1.0	2+	0	0	132.0		1.15	0.95	0.027	0.047	0.017	63.0	41.0	8.3	53.0
	143	510	1.0	+	0	0	224.0	10%	1.39	1.17	0.044	0.064	0.014	84.0	50.0	8.3	54.0
	144	400	1.0	2+	0	0			1.35	1.13	0.018	0.1	0.026	75.6	51.5	8.2	52.1
	145	450	0.5	+	0	0			0.95	0.38	0.05	0.07	0.005	125.0	107.0	7.9	35.0
	146	300	0.5	+	0	0			1.40	1.16	0.06	0.06	0.03	200.0	160.0	7.9	34.2
147*																	
148*																	

\* Animal died Pathology of kidney, mixed acute and chronic change

is not an index of the functional ability of the kidney nor of the extent of the kidney damage present<sup>13</sup>

The total nitrogen and the urea nitrogen of the urine bore a fairly constant relationship to each other throughout these experiments. Immediately following the injection of uranium both decreased in amount. From the second to the fourth day they began to increase,

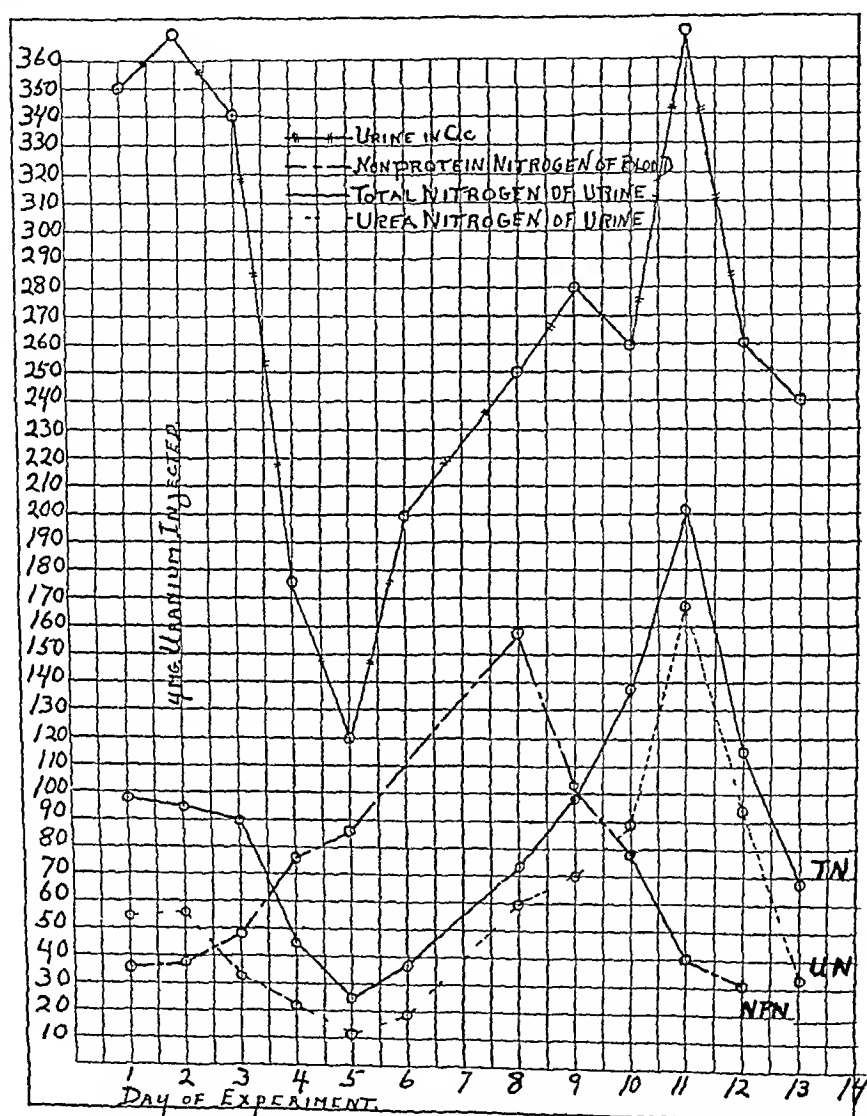


Fig 1—Changes in the nonprotein nitrogen of the blood and in the total nitrogen, urea nitrogen and the amount of urine following an injection of 4 mg of uranium in Rabbit 5

reaching a maximum amount in the urine two or three days after the nonprotein nitrogen in the blood was highest, then gradually returning to normal (Fig 1). The total nitrogen of the urine was frequently

<sup>13</sup> Moschowitz, E. Clinical and Anatomic Relations in Chronic Nephritis, Arch Int Med 24 259 (Aug) 1920

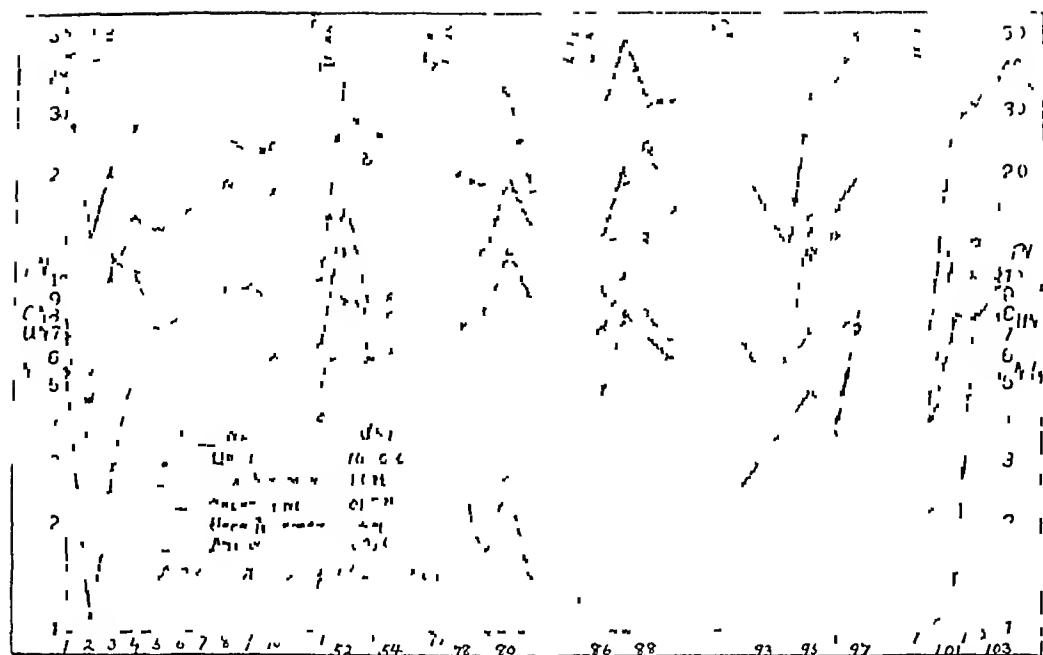


Fig 2—Illustrating the marked similarity in the variation of the amounts of the total nitrogen, urea nitrogen, ammonia, organic acids and the total urine, following repeated injections of uranium, when charted on logarithmic paper (Rabbit 4)

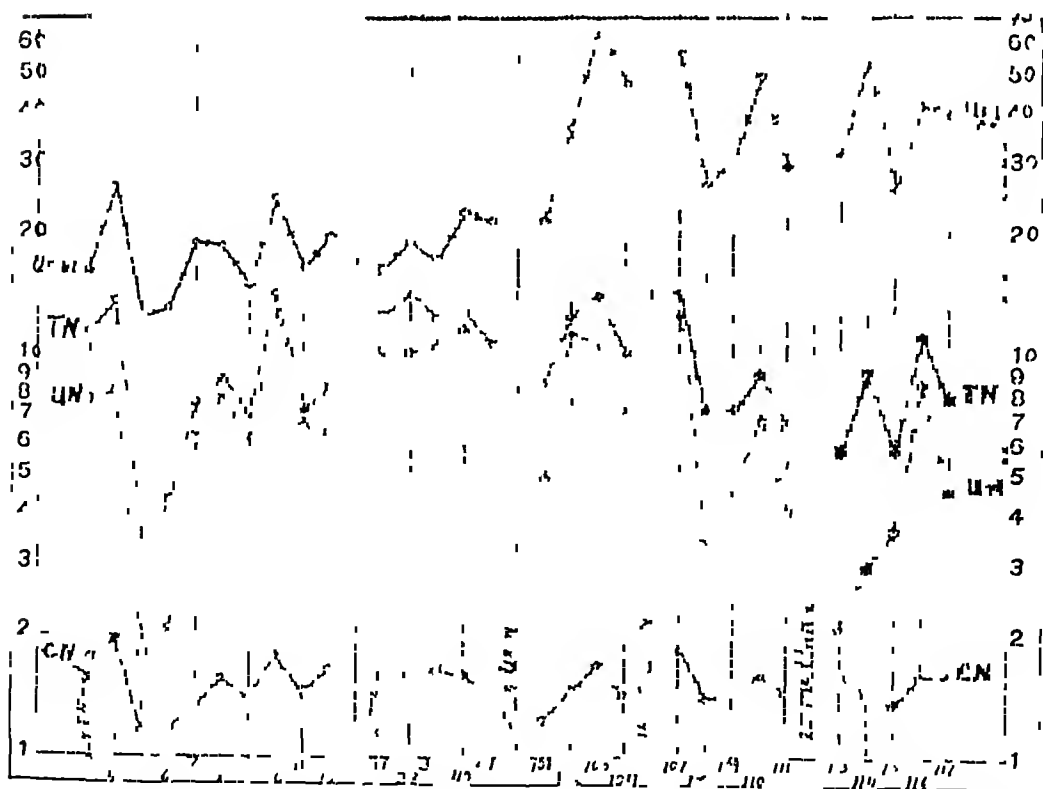


Fig 3—The same curves as in Figure 2 when plotted from data obtained from Rabbit 6

increased to twice its normal amount. The highest reading obtained was 3.34 gm in a twenty-four hour specimen of urine of which the normal reading was 1.15 gm. The urea nitrogen in this same experiment and on the same day was 3.15 gm in a twenty-four hour specimen of urine, whereas its normal level was 0.92 gm. The curves representing the increase and decrease in the amounts of total nitrogen, urea nitrogen, the organic acids and ammonia in the urine and the curve representing the total amount of urine were quite uniformly proportionate when plotted on logarithm paper (Figs 2, 3, and 4). These changes were uniform enough so that by following two of these urinary constituents a fair idea of the kidney activity was obtained.

Traces of acetone and diacetic acid were present in the urine following the initial doses of uranium nitrate in only two rabbits. Following

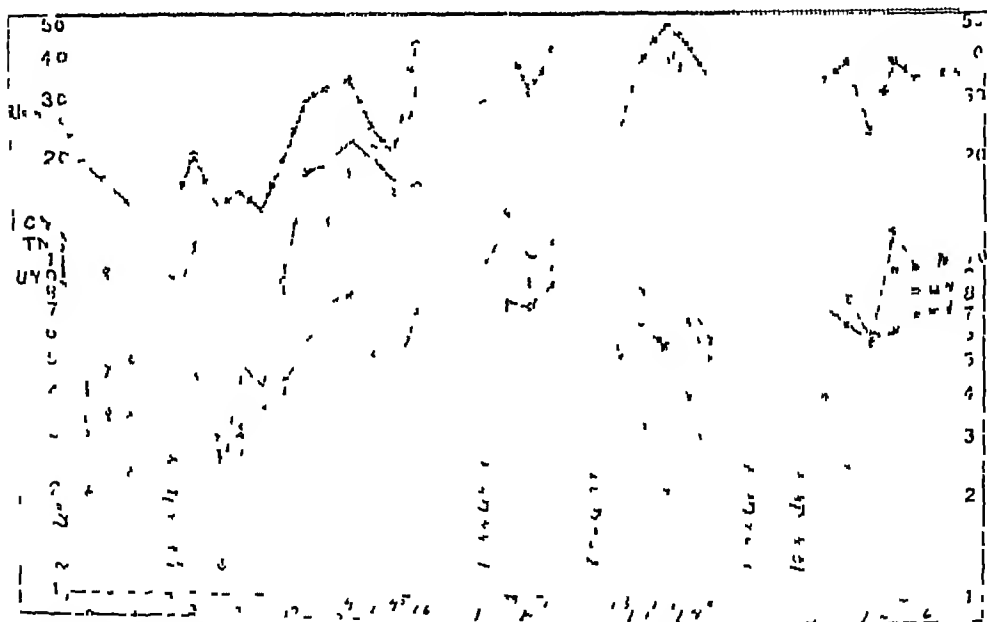


Fig 4—The same curves as in Figure 2 when plotted from data obtained from Rabbit 3

the larger doses they were quite regularly present in amounts varying from a trace to three plus. In one instance, however, following an injection of 40 mg of uranium nitrate, as a result of which the carbon dioxide of the blood serum ranged from 25.5 to 33 volume per cent and the alkali reserve fell as low as 7.6, there occurred no trace of either acetone or diacetic acid. This is not in accord with the belief of MacNider that the toxicity of uranium is dependent on its ability to produce organic acids and acetone bodies.<sup>14</sup>

14 MacNider, Wm de B. The Inhibition of the Toxic Effect of Uranium Nitrate by Sodium Carbonate and the Protection of the Kidney Acutely Nephropathic from Uranium from the Toxic Action of an Anesthetic by Sodium Carbonate, *J Exper M* 23 171 1916

The creatinin and urea acid nitrogen of the urine showed less gross deviation from the normal than any of the constituents studied. But when the changes were charted on logarithm paper they were found to be proportionately as marked as any of the other constituents. However, in one animal (Rabbit 3), both were slightly decreased throughout the entire experiment which ran 175 days. At the end of this experiment the phenolsulphonephthalein output was reduced to 10 per cent in two hours. Pathologically, these kidneys presented the most marked chronic change of any of the series, as is shown in the pathological report.

*Blood Chemistry*—Following the initial injection of uranium nitrate, each animal reacted with a sharp rise in the nonprotein nitrogen and the urea nitrogen of the blood. These increased amounts reached a maximum from the fourth to the seventh day and then gradually

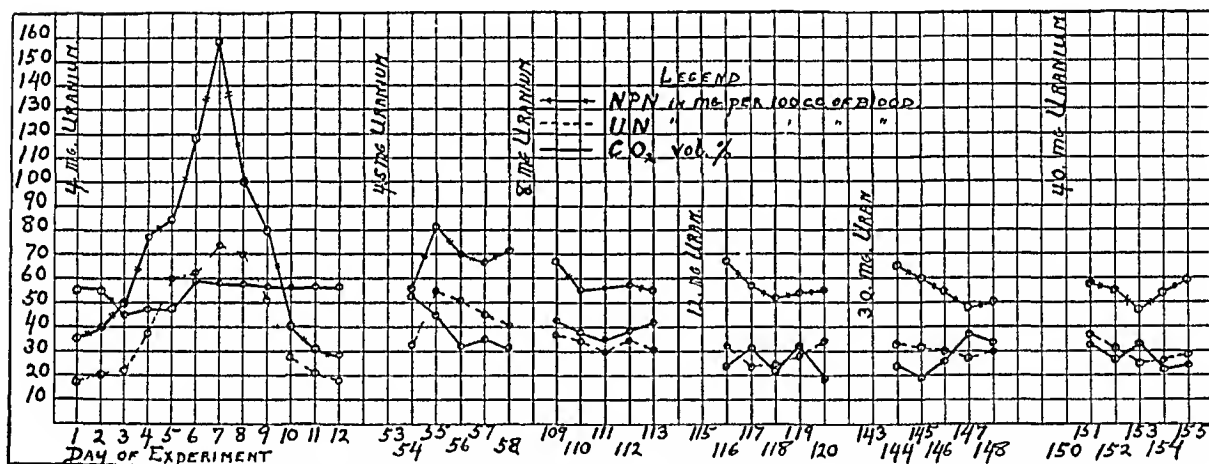


Fig 5—The changes of the nonprotein nitrogen, the urea nitrogen and the carbon dioxide of the blood following repeated injections of uranium (Rabbit 5). The similarity of the curves of the nonprotein nitrogen and the urea nitrogen is apparent. The continued disturbance of the acid-base balance is shown by the curve of the carbon dioxide of the blood serum.

receded. The highest figures obtained were 301 mg nonprotein nitrogen and 215 mg urea nitrogen per hundred cubic centimeters of blood and followed an injection of 4.5 mg uranium nitrate in a rabbit weighing 7 pounds. Following the second injection in each of the animals, the rise of the nonprotein nitrogen and of the urea nitrogen was not so pronounced. Succeeding injections, although the amount of uranium became as high as 50 mg, often resulted in a comparatively small increase in these constituents (Fig 5). However, during all of this time a chronic nephritis was present and the nonprotein nitrogen and the urea nitrogen had reached and maintained a level much higher than normal.

*Acid Base Equilibrium*—As a contrast to the changes in the non-protein nitrogen and the urea nitrogen readings, the disturbance of the acid-base equilibrium became more marked following each injection (Fig 6). In some unpublished work we have found, as had MacNider,<sup>15</sup> that readings of the carbon dioxide and alkali reserve begin to fall at about the twelfth hour following the injection of uranium, and that the curves continued downward from this time. The disturbance of the acid-base balance seems to precede any other change in either the blood or urine. It also appears to precede any histologic change in the kidney or the liver, excepting, possibly, an increased amount of fat in certain of the liver and kidney cells. In the liver the cells about the periphery of the lobule show an apparent increase in the amount of stainable lipid material eighteen hours following the uranium injection. In the cells lining the loops of Henle and the convoluted tubules of the kidney there is, likewise, an increase in the amount of stainable lipid

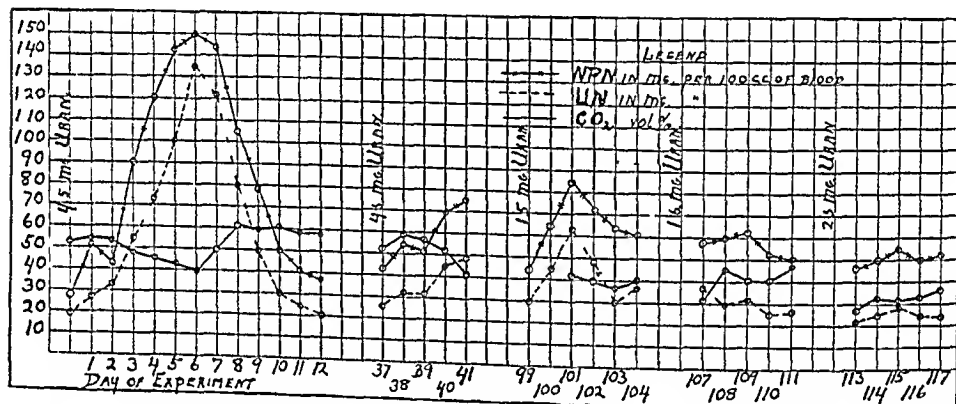


Fig 6—Curves illustrating the same changes as in Figure 5, obtained from data from Rabbit 6

at this time. When the total fat in the liver is extracted with ether in a Soxhlett apparatus, we have found a definite increase as compared with the amount of fat in control rabbit livers. Likewise, we have found the total fat of the kidney to have increased within eighteen hours following the uranium intoxication. This increase in the total amount of fat continues up to forty-eight or even seventy-two hours, apparently reaching a maximum within seventy-two hours.

In rabbits that die following a single injection of uranium, the carbon dioxide and the alkali reserve reach low figures and the excretory functions of the kidney are practically suspended. The organic acids of the urine in one such instance increased from 90 degrees in twenty-four hours to 426 degrees in twenty-four hours, during the last few

<sup>15</sup> MacNider Wm de B. Concerning the Amount of Distribution of Stainable Lipoid Material in Renal Epithelium in Normal and Acutely Nephropathic Animals with Observations on the Functional Response of the Kidney, Proc Soc Exper Biol & Med **11** 1922

days of life, while the ammonia increased from 0.003 gm to 0.053 gm and the creatinin from 0.039 gm to 0.099 gm in the twenty-four hour specimens of urine. The statement has been made that the ammonia does not increase in the urine in patients with chronic nephritis associated with acidosis.<sup>10</sup> This statement does not hold for experimental uranium nephritis in rabbits. The increase of creatinin in the urine is an expression of the kidney effort to excrete this substance which is accumulating in the blood. Its accumulation in the blood has proved of dependable prognostic value.

When a chronic nephritis had resulted from repeated injections of uranium, a persistent acidosis was established in all of our animals. In one instance the carbon dioxide never became higher than 35 volumes per cent from the one hundred and sixteenth to the one hundred and

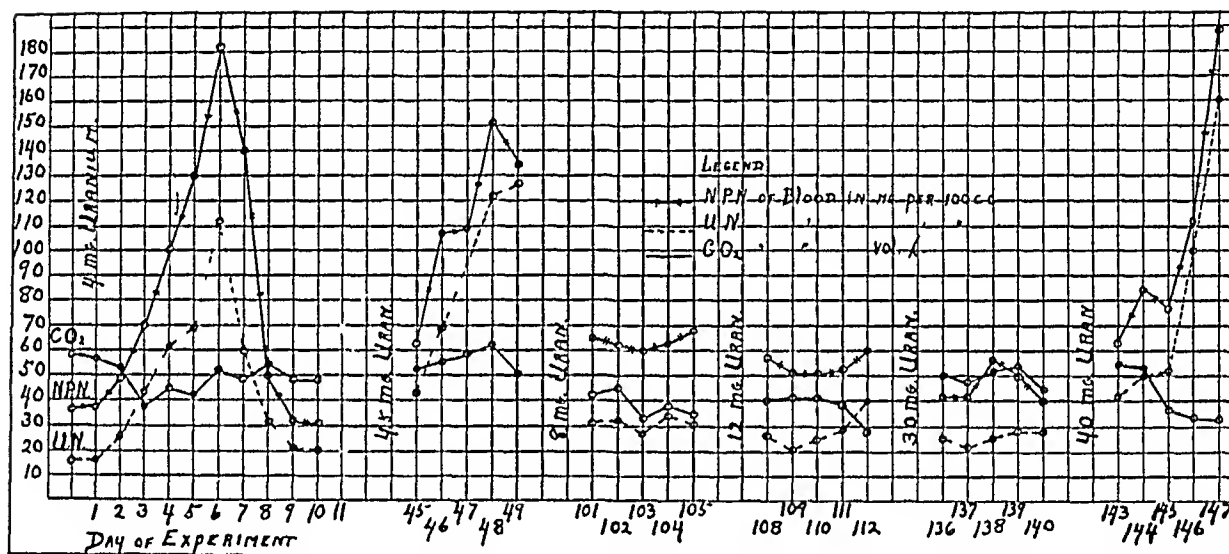


Fig 7—Curves similar to those of Figure 6 obtained from data on Rabbit 1. In this single instance there was a marked increase in the nonprotein nitrogen and the urea nitrogen following the final injection of uranium on the one hundred and forty-third day.

fifty-fifth day of the experiment, at which time the animal was killed (Rabbit 5). During this time the organic acids of the urine ranged from 216 to 480 degrees.

The ammonia of the urine was little altered as a result of the milder intoxications, but during the latter course of the experiments it was increased from ten to forty times with a maximum increase of eighty times.

The organic acids of the urine were followed throughout these experiments to see how accurate an index this method gave as to the

16 Marriott, W. McK. and Howland, J. The Influence of Acid Phosphates on the Elimination of Ammonia in the Urine, Arch. Int. Med. 22: 477 (Oct.) 1918.



degree of acidosis    Normal readings in nonnephritic rabbit urines varied from 90 to 120 degrees acidity    Whenever an acidosis was present, as evidenced by the alkali reserve and carbon dioxid readings, there was an increase in the organic acids    This increase was most marked at the time of greatest acidosis    But the total amount of acids seemed to bear a more uniform relation to the total amount of urine (Fig 8), and did not follow the alkali reserve and carbon dioxid readings closely enough to make this test as dependable as the latter    The

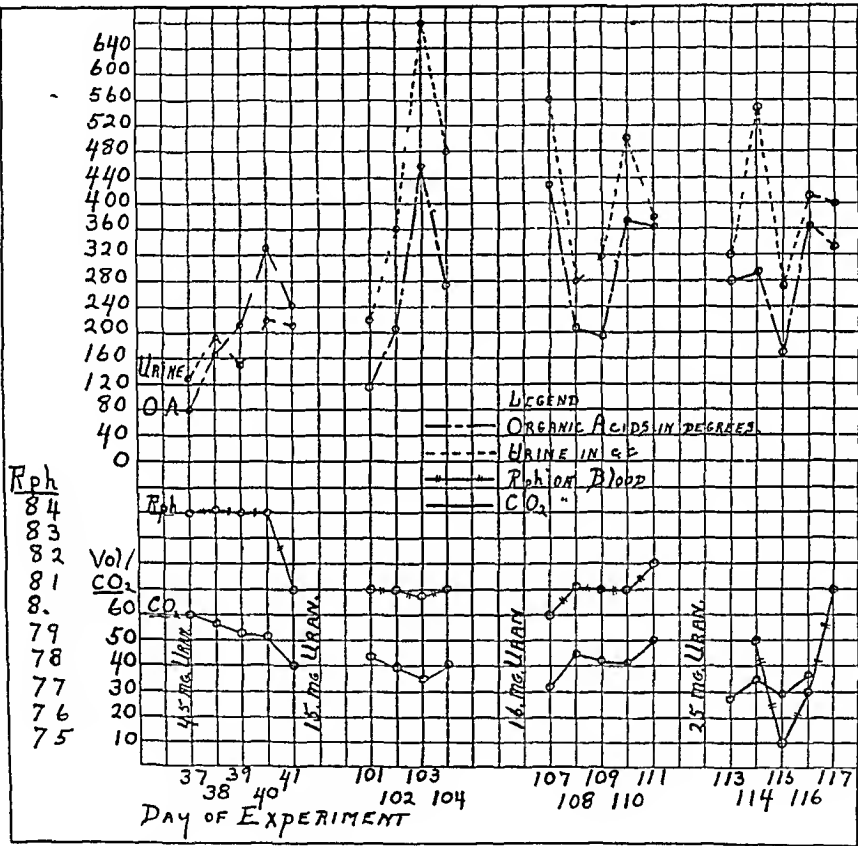


Fig 8—Illustrating the similarity of the curves representing the total amount of the urine to the organic acids of the urine    The relationship of the curves of the alkali reserve to the carbon dioxid of the blood serum is also shown (Rabbit 6)

ease of doing the organic acid test as compared with the technic of the alkali reserve and carbon dioxid would tend to make the former a more popular method, provided it gave as accurate results

*Pathology*—The gross changes were limited to the kidneys    When an animal died of a single dose of uranium, the kidneys were enlarged and of a pale color    The capsule stripped easily, leaving a smooth surface    The cut surface bulged    The cortex was increased in width and its markings were indistinct

The kidneys from animals that were killed after having received many doses of uranium were not enlarged. The capsule usually stripped with some difficulty, leaving a slightly rough surface. On cut section no notable change was observed. The microscopic findings were much more marked.

#### PROTOCOL OF EXPERIMENTS

**RABBIT 1**—This animal had received a total of 985 mg of uranium over a period of 147 days and was killed six days following the last dose of 40 mg. The sections have a patchy appearance. The tubules which were damaged early in the experiment are lined with rows of low cells with irregular nuclei which often push the inner edge of the cell into the lumen of the tubule. The lumen of the tubule in such instances is increased in width. Adjacent to this group are tubules with cells so swollen that the lumen is entirely filled. There are hyaline casts in many of the collecting tubules. Between the cortex and medulla, especially about the blood vessels, fibroblasts are numerous. On the whole, however, there is little connective tissue increase. The glomerulae are not altered.

**Summary** Mixed, acute and chronic degenerative changes.

**RABBIT 2**—A total of 31 mg of uranium was injected over a period of seventy-four days. Throughout the entire cortex are scattered many round cells. There is an increased cellularity of the glomerular tufts. The endothelial cells lining the tuft capillaries are swollen so that the lumen of the capillaries is compressed and contains less blood than usual. There is an exudate between Bowman's capsule and the tuft. The cells of the convoluted tubules are swollen so that the lumen is filled. The nuclei stain poorly and the cell cytoplasm has a milky, pale, structureless appearance.

**Summary** Acute degenerative changes involving the convoluted tubules and the glomerulae.

**RABBIT 3**—In this case 505 mg of uranium were given over a period of 175 days. The tubules are dilated and are lined by low epithelial cells. They frequently contain hyaline casts. The cytoplasm of these cells is granular and the nuclei are irregular in shape and size and occupy various positions in the cell. There is a sharp infiltration of round cells especially about some of the glomerulae and along the limbs of Henle. The round cells are epithelioid in character, with large nuclei. There are also some leukocytes. There is also a round cell infiltration of a lesser degree about some of the collecting tubules. The glomeruli are crowded together in many instances and vary markedly in size. Bowman's capsule is thickened in some instances. There is an increase of fibroblasts in the tuft so that it is more cellular than normal. There is an actual increase of fibrous connective tissue throughout the cortex. These kidneys present, then, a marked increase in fibrous connective tissue, atrophy of some tubules, dilatation of others and chronic cellular change in others. This is an excellent example of chronic change.

**RABBIT 4**—This animal received, over a period of 103 days, a total of 81 mg of uranium, 50 mg having been given two days before death. These kidneys present an extreme, acute degeneration. The cells lining the convoluted tubules and the ascending and descending loops of Henle are so swollen that the entire tubules are filled, the cell outlines are obliterated and the nuclei themselves are for the most part not visible. These changes are so evident that patches of the section appear solid gray, the glomerulae in these portions being surrounded by such filled up patches. The glomeruli contain fine hyaline-like bodies in the capillary walls (Councilman's bodies). This is the only instance in which these bodies are found.

The tubules in the outer portion of the cortex are much less involved, although their lumens are filled with necrotic material and the cells themselves are less well defined than usual.

Summary Extreme, acute degenerative changes in the tubules with hyaline droplets in the glomerular tufts

RABBIT 5—Over a period of 155 days 98.5 mg of uranium were injected. The convoluted tubules and the loops of Henle present evidence of moderate chronic change. Low irregular cells line the tubules. There are many hyaline casts in the tubules. There are scattered areas of round cell infiltration representing beginning fibrosis. There is a proliferation of the capillary epithelium with less blood than usual in the tufts. There is also a slight thickening of Bowman's membrane.

Summary Moderate chronic change

RABBIT 6—The total amount of uranium injected over a period of 136 days was 65 mg. The convoluted tubules have, for the most part, undergone chronic changes, as heretofore described. The cells lining the tubules are lower than normal. The nuclei take up a proportionately larger amount of space. Many tubules are compressed or atrophied. Many other tubules are dilated. Among these dilated and compressed tubules is a considerable round cell infiltration. The atrophy of many tubules and the dilatation of others make it appear as if the glomeruli were closer together than normal. Some of the convoluted tubules present moderate acute change, the lumen being filled with necrotic debris.

Summary Chronic change with a minimum of acute degeneration

#### DISCUSSION

The kidneys of rabbits that died following a single injection of uranium presented extreme changes in the cells lining the convoluted tubules. In some instances this consisted of swelling of the cells until the lumen of the tubule was obliterated. The cells themselves contained many fine granules and the nuclei were indistinct. In other instances cells were loosened from the tubules and the nuclei were indistinct or or could not be found. Still further injury was found consisting of necrosis of a large proportion of the cells lining many of the convoluted tubules. In such instances the functions of the kidney were practically suspended with the result that there was a marked increase in the nonprotein nitrogen and the urea nitrogen of the blood. At the same time, there was a marked disturbance of the acid-base balance, the alkali reserve and the carbon dioxide of the blood becoming gradually lower until death. If, however, the animal does not succumb and repair or replacement of the damaged cells lining the convoluted tubules takes place, an altered cell results. This cell is not so large as its predecessor. Its nucleus is larger in proportion to the size of the cell than formerly and often pushes the outer edge of the cell toward the lumen of the tubule. These changes have been described by MacNider<sup>17</sup> and others. Frequently, young animals are able to so completely repair this damage that the acid-base equilibrium returns to normal and the only evidence of kidney damage that may remain is a slightly lowered phthalein output or traces of albumen in the urine.

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17 MacNider, William de B. A Pathologic Study of the Naturally Acquired Chronic Nephropathy of the Dog, *J. M. Research* 34 177, 1916

But, following repeated injections of uranium, there occur, in addition to the changes in the cells lining the convoluted tubules and the limbs of Henle, changes in the glomeruli, Bowman's capsule and the walls of the capillaries. Further, a diffuse round cell infiltration takes place throughout the cortex and following this there is an actual deposition of scar tissue in these areas. If the experiment is carried on for a sufficient length of time, a pronounced chronic nephritis which resembles chronic diffuse nephritis in man, results. During the development of this nephritis and after its establishment a disturbed acid-base balance persists. During the acute exacerbations there has been a heaping up of nonprotein nitrogen and urea nitrogen in the blood. At the same time there has been a diminution in the total nitrogen, urea nitrogen and to a less extent of the creatinin and uric acid nitrogen in the urine. This is followed in from four to five days by an increased excretion of these substances and a gradual fall of the heaped up products in the blood. When the chronic nephritis is established a moderate increase in the nonprotein nitrogen and urea nitrogen persists but, at the same time, there is an increase in the excretion of the various urinary constituents.

MacNider<sup>18</sup> observed that the first change in experimental nephritis induced by uranium has been a disturbance of the acid-base balance. He has also shown that there is a close relation between the acid-base balance and the ability of the kidney to continue its functions as determined by the various functional tests and the blood and urine chemistry. Our work has corroborated this. As stated before, we have found that lowered carbon dioxide and alkali reserve readings precede any other change. Whether this disturbed balance effects the early histologic changes that occur in the liver and kidney cells has not been proved, but it seems very probable.

Whether a disturbed acid-base balance has an etiologic relationship to beginning interstitial nephritis in man is a pertinent question. The urines of patients with chronic interstitial nephritis are strongly acid. They frequently have hydrogen ion concentrations of from 5.5 to 6. Sansum<sup>19</sup> has been able to correct this by a basic diet. When this is effected such patients whose blood pressures are increased often have a decided fall in both the systolic and diastolic readings. These lowered readings have been maintained for months at a time in patients whom we have followed. Whether further degenerative changes in an interstitial nephritis can be deferred by keeping the reaction of the urine at or

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18 MacNider, William de B. The Changes Induced in the Kidney When an Acute Injury Is Superimposed in a Chronic Glomerulonephropathy. A Functional and Pathologic Study, *Southern M. J.* **14** 357, 1921.

19 Sansum, W. D. The Use of Basic Diets in the Treatment of Nephritis, *California State J. M.* **20** 1, 1922.

about the neutral point, that is, a hydrogen ion concentration of 7, is an interesting question. In endeavoring to answer it one must be mindful of the long periods of latency that frequently occur without any kind of treatment.

The relation between the nonprotein nitrogen and the urea nitrogen of the blood is a definite one in human interstitial nephritis. We have found this to be so in experimental uranium nephritis. Normally the urea nitrogen is 50 per cent of the nonprotein nitrogen, but as the nonprotein nitrogen increases in amount, the urea nitrogen increases at a faster rate, so that when the nonprotein nitrogen reaches 100 mg per hundred cubic centimeters of blood, the urea nitrogen is then usually about 85 per cent of the nonprotein nitrogen.

The phenolsulphonephthalein readings at the beginning of our experiments varied from 80 to 91 per cent output in two hours. The rabbit at the time of the injection of the phenolsulphonephthalein had 75 cc of water by stomach tube. During the latter stages of our experiments, the phenolsulphonephthalein readings varied from 10 to 18 per cent. For a few days following some of the larger injections the output was lower than this.

Christian<sup>20</sup> has recorded a fall in the phenolsulphonephthalein in acute nephritis in patients when they start to improve clinically. We did not make phenolsulphonephthalein determinations frequently enough to determine this, but in some of our animals we observed a secondary acidosis after an animal started to recover. It is interesting to note that MacNider,<sup>21</sup> working with dogs, also discovered a secondary fall in phenolsulphonephthalein after the animal began to recuperate from the uranium intoxication.

#### CONCLUSIONS

Varying stages of nephritis in rabbits have been produced by the injection of uranium nitrate. Large single doses have produced an extreme degeneration of the cells lining the convoluted tubules and the loops of Henle. Repeated doses over a long period of time have produced a chronic nephritis, comparable to chronic diffuse nephritis in man.

After repeated injection, very large doses of uranium may be given. This dosage reached 50 mg of uranium nitrate in a 6 pound rabbit.

Initial injections of uranium resulted in a sharp rise in the nonprotein nitrogen and the urea nitrogen in the blood. After a chronic nephritis

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20 Christian H A. Some Phases of the Nephritis Problem, *Am J M Sc* 151:625, 1916.

21 MacNider, William de B. A Functional and Pathologic Study of the Chronic Nephritis Induced in a Dog by Uranium Nitrate, *J Exper M* 29:513, 1919.

had been established, these constituents were continuously higher than normal, but were often little altered following the injection of from 40 to 50 mg of uranium

When charted on logarithmically ruled paper, the total nitrogen, urea nitrogen, and the uric acid nitrogen in the urine are all roughly proportionate in their variations among themselves and to the amount of urine in cubic centimeters

The organic acids in the urine are also roughly proportionate to the foregoing

The increases and decreases of the ammonia in the urine follow the direction of the curves of the foregoing but in an exaggerated way, generally dropping lower and rising higher (proportionately) than the others

The curve for the urea nitrogen in the urine is somewhat flatter than the others, dropping and rising less, but in the same general direction

The nonprotein nitrogen, urea nitrogen and carbon dioxide in the blood do not parallel any of the above curves. The nonprotein nitrogen and the urea nitrogen follow each other closely. Either would seem as satisfactory as the other in determining the kidney's excretory ability

The creatinin and uric acid nitrogen of the urine showed less deviation from the normal than any of the constituents studied

Acetone and diacetic acid were irregularly present in the urine following the uranium injections

The first change following an injection of uranium was found to be a disturbance of the acid-base balance. At about the same time certain histologic changes were found in the liver and kidney

The organic acids of the urine, while a fair index of the degree of acidosis, were not found as dependable as the alkali reserve and carbon dioxide of the blood serum

The relative degree of acidosis as determined by the carbon dioxide and alkali reserve readings and by the increased output of organic acids and ammonia in the urine coincided pathologically with the extent of cell destruction in the kidney

# THE VITAL CAPACITY IN HYPERTHYROIDISM WITH A STUDY OF THE INFLUENCE OF POSTURE

A PRELIMINARY REPORT <sup>×</sup>

I M RABINOWITCH, M D

MONTREAL

The data presented here form part of the observations made on the vital capacity in cases of hyperthyroidism. Although a number of such observations have been made in a wide range of similar cases of varying severity, it would be unwise at the present time to formulate definite conclusions of too sweeping a character. Sufficient has, however, been done to demonstrate the clinical utility of the test, and to stimulate further studies.

Although this laboratory procedure is old<sup>1</sup> it has not received, relatively, the same consideration as have many other laboratory methods. This, in great part, was due to the lack of knowledge of certain factors which must govern the interpretation of findings, presenting such wide, and at times irregular variations, even in the normal subject. The very thorough work of Dreyer, Peabody and Wentworth, Lundsgaard and Van Slyke, and West<sup>2</sup> in establishing "normals" as units for comparison demonstrates that this simple laboratory procedure is a satisfactory means of estimating the general physical status of a person. Whether the diminution of the vital capacity is due to physical factors, such as diminution of the lung volume, loss of elasticity of lung tissue, etc., or to chemical changes which influence the respiratory center, etc., is still problematic. This, however, does not vitiate the clinical value of the test.

Observations, some of the data of which are shown, were made in three groups of cases: (a) hyperthyroidism of the exophthalmic goiter type, (b) hyperthyroidism secondary to previously existing adenoma, and (c) hyperthyroidism following the administration of thyroid extract. The purpose in this report is to show, graphically, the general relation that has been found between the degree of hyperthyroidism as estimated by the basal metabolic rate and the vital capacity. The detailed results of these studies, in which an

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\* From the Department of Metabolism, Montreal General Hospital.

1 Hutchison, J. On the Capacity of the Lungs and on the Respiration Functions, with a View of Establishing a Precise and Easy Method of Detecting Disease by the Spirometer, *Med Chir Tr Lond* **29** 139, 1846.

2 West H F. Clinical Studies on Respiration, *Arch Int Med* **25** 306 (March) 1920. Dreyer, G. The Assessment of Physical Fitness, London, Cassell & Co., Lundsgaard C, and Van Slyke, D D. The Relation Between Thorax Size and Lung Volume, *J Exper Med* **27** 65, 1918. Peabody, F W, and Wentworth, J A. Clinical Studies on Respiration, *Arch Int Med* **20** 443 (Oct) 1917.

attempt is made to determine the factors which operate in determining the vital capacity and in which the clinical pictures are analyzed and correlated with the laboratory findings form part of a report to be published separately, with the accumulation of more data

The determination of the value of any physical property is always subject to error, so that the results of observations made even under the most ideal conditions can be but approximations of the true values. The chief sources of error are (a) errors of observations, (b) errors of the apparatus used, and (c) neglect of certain other factors which exercise an appreciable effect on the results. Although the first two may be controlled with a reasonable degree of accuracy in the estimation of the vital capacity, the last is of special importance for consideration, since at times the clinical condition demands that the patient be disturbed as little as possible. Thus, it was not always practical to place the patient in the most suitable posture for the test. Results obtained in an abnormal posture must necessarily lead to results varying from the "normal" even in the healthy subject.

Therefore, a series of values for the vital capacity were obtained in the normal posture, and in a standard recumbent posture, with the subject in the dorsal decubitus position, and the head and shoulders elevated at an angle of about 30 degrees. This was done with the intention of deriving a constant whereby it might be possible to calculate the normal vital capacity, where it is clinically possible to determine the latter only in the recumbent position. For this purpose a table of values was drawn showing the vital capacity in the normal position, in the recumbent position, and the percentage which the normal is of the recumbent, that is,  $\frac{\text{normal vital capacity}}{\text{recumbent vital capacity}} \times 100$ . The normal male subjects were members of the hospital staff and medical students. The normal female subjects were undergraduate nurses assumed to be healthy, having had a thorough physical examination before admission to the training school for nurses. The vital capacity was measured with a spirometer which gave readings within an error of 5 c c. The procedure necessary to obtain results was first demonstrated to the subject, and the maximum reading of five determinations was accepted as the final result. Since it was necessary to determine the body surface in the calculation of the basal metabolic rate, it seemed practicable to apply this unit in the calculation of the vital capacity.

The method of obtaining the body surface was that of DuBois and DuBois.<sup>3</sup> Calculated on the basis of liters of air expired per square meter of body surface, it will be noted in column 7 that the average result obtained was 1.93 for females. This approximates very closely that obtained by West<sup>2</sup> which was 2.07. The standard adopted, there-

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<sup>3</sup> DuBois, D., and DuBois, E. F. The Measurement of the Surface Area of Man, *Arch Int Med* 15: 868 (June) 1915



fore, that of West,<sup>2</sup> was 20 for females and 25 for males. On this basis, 88.9 per cent of the normal subjects in the normal posture showed a vital capacity within the limits of normal variation allowed,  $\pm 10$  per cent. The combined results obtained by employing the above units

TABLE 1—Data of Fifty Cases Influence of Posture on Vital Capacity

Number	Name	Vital Capacity in Normal Posture (a)	Vital Capacity in Recumbent Posture (b)	$\frac{a}{b} \times 100$	Body Surface, Sq. M. (c)	$\frac{a}{c}$	Calculated Vital Capacity
1	HV	3,230	3,010	107.3	1.60	2.01	3,235
2	PS	3,220	3,000	107.0	1.75	1.84	3,225
3	AR	2,960	2,890	102.4	1.51	1.96	3,106
4	ABF	3,310	3,210	103.1	1.56	2.12	3,450
5	KW	3,350	3,230	103.7	1.78	1.88	3,472
6	AC	3,450	3,270	105.5	1.69	2.04	3,515
7	CD	3,100	2,820	109.9	1.49	2.08	3,031
8	SM	3,430	3,180	107.8	1.59	2.11	3,418
9	HI	3,170	2,910	108.9	1.65	1.92	3,128
10	MI	3,530	3,350	105.3	1.65	2.14	3,601
11	AE	2,860	2,840	100.3	1.52	1.88	3,053
12	GA	2,440	2,440	100.0	1.85	1.31	2,623
13	GO	3,075	2,925	105.1	1.45	2.12	3,144
14	NEP	3,190	2,990	106.6	1.66	1.92	3,214
15	LJG	3,090	2,990	103.3	1.82	1.69	3,214
16	CC	3,300	2,900	113.7	1.62	2.03	3,117
17	TLO	3,200	2,930	109.2	1.86	1.72	3,149
18	DDA	2,790	2,690	103.7	1.50	1.86	2,591
19	AMF	3,415	3,415	100.0	1.76	1.93	3,671
20	ABW	2,875	2,525	113.8	1.56	1.83	2,714
21	LJS	3,040	3,040	100.0	1.46	2.08	3,268
22	OE	3,400	3,100	109.6	1.77	1.92	3,332
23	OM	3,760	3,685	102.0	1.92	1.95	3,961
24	MHH	3,660	3,460	105.8	1.68	2.17	3,719
25	MON	3,065	2,565	119.4	1.58	1.93	2,757
26	IMO	3,820	3,620	105.5	1.86	2.05	3,511
27	ANH	2,350	1,850	127.0	1.55	1.51	1,938
28	GS	3,180	2,880	110.4	1.69	1.88	3,096
29	GMD	3,420	2,920	117.1	1.78	1.92	3,139
30	EMH	3,365	2,990	112.5	1.70	1.98	3,214
31	FCS	3,765	3,740	100.6	1.44	1.91	4,020
32	WAS	3,190	2,240	116.4	1.53	2.01	2,455
33	R	4,875	4,775	102.0	1.30	2.11	5,133
34	ZAS	3,010	2,760	109.0	1.55	1.94	2,867
35	MDE	3,400	3,000	113.3	1.72	1.98	3,225
36	IGJ	3,195	3,195	107.5	1.63	1.95	3,434
37	IS	2,485	2,385	104.1	1.43	1.69	2,563
38	CD	3,220	2,970	108.2	1.52	2.11	3,692
39	McG	4,245	3,995	106.2	1.74	2.43	4,294
40	LD	3,290	2,890	113.8	1.75	1.88	3,106
41	FJ	2,870	2,270	126.4	1.56	1.84	2,440
42	EVB	2,645	2,645	100.0	1.52	1.74	2,843
43	MOJ	3,155	3,105	101.5	1.61	1.95	3,337
44	NCM	3,050	2,950	103.3	1.43	2.06	3,171
45	SAB	3,090	3,090	100.0	1.68	1.83	3,321
46	ALF	2,625	2,110	124.8	1.53	1.75	2,268
47	SR	3,530	3,460	102.0	1.84	1.92	3,742
48	GP	3,650	3,600	100.6	1.72	2.14	3,934
49	LS	3,270	3,060	106.9	1.65	1.98	3,289
50	APM	2,750	2,720	101.2	1.48	1.85	2,924

were (a) Within normal limits, 88.9 per cent, (b) between 80 and 90 per cent of normal 4.4 per cent, (c) between 80 and 85 per cent of normal 2.2 per cent, (d) between 75 and 80 per cent of normal 2.2 per cent, (e) between 120 and 125 per cent of normal 2.2 per cent.

Column 4 shows the results of fifty analyses made in the recumbent position. With the exception of five subjects in this group in whom no difference was noted, the effect of the recumbent position was to diminish the air expired from 20 to 600 c.c. Although in many cases

the difference is not of sufficient magnitude to affect the results from a clinical point of view, it seemed that a greater value could be attached to them, if it were possible to adopt a constant correction, whereby the actual and calculated values would vary within narrower limits

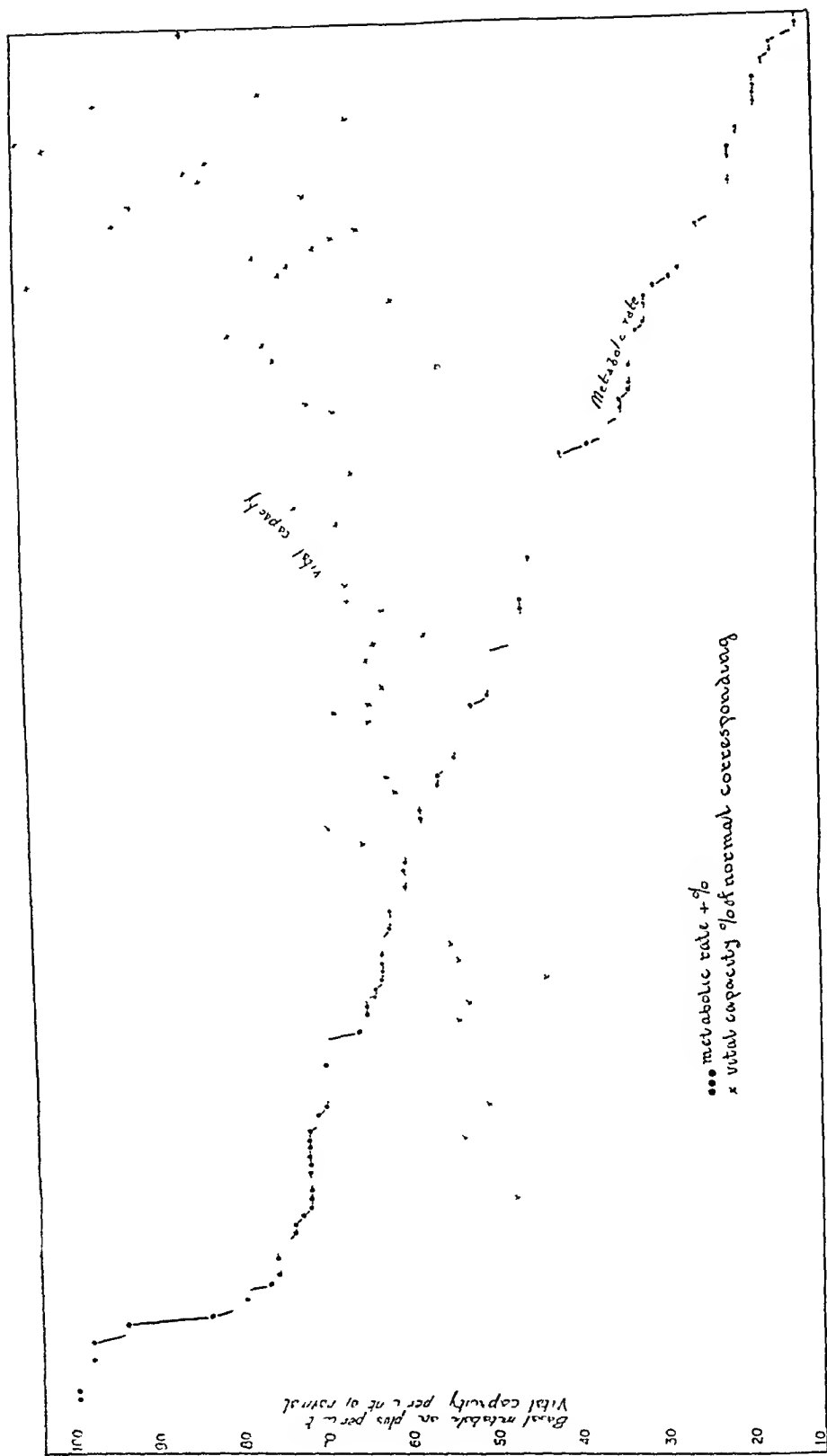
The arithmetical mean of all values for the factor  $\frac{\text{normal vital capacity}}{\text{recumbent vital capacity}} \times 100$  was 107.5, that is the vital capacity obtained in the normal posture was 7.5 per cent greater than that obtained in the recumbent posture. Mathematicians have for years known, and Krogh<sup>4</sup> has recently pointed out that the average of a series of measurements (i.e. the arithmetical mean) is not the most probable true value. The most probable true value is arrived at by the application of the statistical theory of errors. In this calculation the minimum regarded as sufficient is the determination of the mean error or standard deviation of a single determination, and the mean error of the average. In these studies this has been considered. When one appreciates the numerous possible factors which might influence the results in the estimation of the vital capacity, however true this may be with regard to the purely arithmetical value of the result, such refined calculation, involving the statistical theory of errors, would probably give an impression that was not intended, that is, the extreme accuracy with which this physical measurement can be made. Since every physical measurement of any description involves some error or can be carried out with only a certain degree of accuracy, it is evident that the number expressing the value of a property depending on a measurement can only be approximate. However finely we may calculate the vital capacity, our results cannot increase the accuracy of the value beyond the limits of experimental error. Therefore, from the observations made, the correction constant accepted was 1.075, that is, the product obtained by multiplying the observed volume of gas expired in the recumbent position by 1.075 was accepted as the volume that would be obtained if the subject were in the normal posture.

It will be noted from the values in column 8 that by applying this correction and thus increasing the observed vital capacity obtained in the recumbent position, the actual (column 3) and calculated (column 8) corresponds remarkably well.

On this basis, 86.4 per cent of the same normal subjects whose vital capacity was taken in the recumbent posture showed variations within the normal limits only, allowing  $\pm 10$  per cent variation. This compares favorably with that obtained in the normal posture—88.9 per cent.

In the graphic chart is shown the general relation between the decrease in the vital capacity and the severity of the hyperthyroidism as estimated by the basal metabolic rate. The latter varied from  $\pm 100$

<sup>4</sup> Krogh, A. The Respiratory Exchange of Animals and Man. Monographs on Biochemistry, London, Longmans, Green & Co.



Relation between decrease in vital capacity and degree of hyperthyroidism as estimated by basal metabolic rate

per cent to + 16 per cent and the vital capacity varied from 30 to 101 per cent of normal. It will be noted that in only three cases was the vital capacity above the normal, and five values were within the normal limits of variation,  $\pm 10$  per cent.

A noteworthy observation was that all patients having a vital capacity of 40 per cent or under of normal were bedridden, which agrees with the observations of Peabody on cases of heart failure. Table 2 shows the average vital capacity found in relation to the metabolic rate.

An additional interest is attached to these observations, since we have here a possible explanation of the dyspnea observed in cases of severe hyperthyroidism, excluding that due to chemical stimulation of the respiratory center or cardiac embarrassment. Peabody<sup>5</sup> first demonstrated that an important factor in producing dyspnea may be the inability to breathe deeply. He studied mathematically the problem of the maximum minute volume of pulmonary ventilation and found that

TABLE 2—Average Vital Capacity in Relation to Metabolic Rate

Metabolic Rate, Percentage Above Normal	Vital Capacity, Percentage of Normal
Between 100-90	43
90-80	46
80-70	50
70-60	57
60-50	63
50-40	65
40-30	71
30-20	79
20	79

the latter was partly a function of the vital capacity. This appears to have an application to hyperthyroidism. Associated with an increase in the basal metabolic rate, the oxygen consumption and the carbon dioxide production increases. To acquire the former and excrete the latter an increase in the pulmonary ventilation, including the respiration rate and ventilation rate, is required. A lower vital capacity may thus be an important factor in the production of dyspnea in severe cases of hyperthyroidism. This problem is being investigated.

<sup>5</sup> Peabody, F W. A Mechanical Factor in the Production of Dyspnea in Patients with Cardiac Disease, *Arch Int Med* **20** 443 (Sept 1917), Sturgis, C C, Peabody, F W, Hall, F C, and Fremont-Smith, F Jr. The Relation of Dyspnea to the Maximum Minute Volume of Pulmonary Ventilation, *Arch Int Med* **29** 236-244 (Feb) 1922, Peabody, F W, Wentworth, J A, and Barker, B I. The Basal Metabolism and the Minute Volume of the Respiration of Patients with Cardiac Disease, *Arch Int Med* **15** 468-478 (Sept) 1917.

# STUDIES ON THE POTASSIUM CONTENT OF HUMAN SERUM\*

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## OBSERVATIONS OF OTHER WORKERS

The normal potassium content of the human blood serum has been determined by different workers with various results, as shown in Table 1. The older writers, Schmidt and Wanach, worked with inferior chemical methods. The more recent workers have all obtained fairly uniform results with the exception of Richter-Quittner whose figures are considerably higher than those reported by others. Richter-Quittner found the concentration of potassium in ashed serum to be considerably higher than that found in the ultrafiltrate from the same serum. He argued from this that a portion of the potassium was bound to serum protein. Kramer and Tisdall, however, have found

TABLE 1—*Potassium Content of Human Serum Found by Various Observers*

	Mg per 100 C c
Schmidt, C, <sup>1</sup> 1850	31-33
Wanach, R., <sup>2</sup> 1888	15-21
Richter-Quittner, <sup>3</sup> 1921	50-80 in ashed serum
	20-60 by the ultrafiltrate method
Macallum, A. B., <sup>4</sup> 1917	19-21 in blood plasma
Meyers, V. C., and Short, J. J., <sup>5</sup> 1921	14-18
Kramer, B., and Tisdall, F. F., <sup>6</sup> 1921	18-21

no discrepancy between the results obtained on ashed serum and those by direct precipitation from the same serum.<sup>7</sup> They have emphasized the remarkable constancy of the concentration of potassium in normal human serum.

A number of investigators have studied the potassium of the serum in pathologic conditions. Schmidt obtained values of from 43 to 72 mg per hundred cubic centimeters of the serum of patients suffering from cholera and 63 mg in a patient with "anasarca without albumin-

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1 Schmidt, C. *Charakteristik der Epidemischen Cholera*, Leipzig und Mitau 1850, pp. 29 and 30.

2 Wanach, R. *Jahresb. d. Thier Chemie* **18** 88, 1888.

3 Richter-Quittner. *Biochem. Ztschr.* **24** 110, 1921.

4 Macallum, A. B. *Tr. College of Physicians, Philadelphia* **39** 286, 1917.

5 Meyers, V. C., and Short, J. J. *J. Biol. Chem.* **48** 83, 1921.

6 Kramer, B., and Tisdall, F. F. *J. Biol. Chem.* **46** 339, 1921.

7 This finding does not contradict the possible existence of compounds of protein with potassium in serum.

uria" Clausen<sup>8</sup> found from 53 to 90 mg potassium in the plasma of patients with various diseases. Kramer and Tisdall reported in twelve children suffering from various febrile diseases values for the potassium of serum ranging from 35 to 70 mg per hundred cubic centimeters. They were aware, however, that the potassium concentration increases when the serum is allowed to remain in contact with the clot and, therefore, suggested that the observed increase of the potassium of the serum of pathologic cases required further investigation. Meyers and Short, on the other hand, could find no increase in the potassium in any of the diseases which they studied. In ten patients suffering from a variety of pathologic conditions such as polycystic kidneys, cardiac decompensation and anasarca, essential hypertension, eclampsia, carcinoma, pneumonia, diabetic coma and syphilis, their values ranged from 15 to 20 mg in all except three instances. These three serums, which gave values of 24, 28 and 35 mg, respectively, had been allowed to stand a considerable length of time before separation from the

TABLE 2—*Potassium Content of Serum at Varying Periods*

Time Before Separating Serum	Potassium, Mg per 100 C c
0	22.5
1 hour	23.6
2 hours	23.6
4½ hours	26.1
9 hours	26.5
24 hours	36.1
48 hours	41.9
72 hours	59.1 slight hemolysis present
96 hours	61.9 slight hemolysis present

clot. The same authors found in seven cases of advanced nephritis, showing marked nitrogen retention, from 10 to 20 mg of potassium per hundred cubic centimeters of serum.

#### SOURCES OF ERROR IN THE ESTIMATION OF POTASSIUM

In this study we have used the method described by Kramer and Tisdall. Because of the higher results obtained by Kramer and Tisdall with the serum of febrile patients, it was decided to investigate further the factors which might lead to errors in the estimation of potassium in the serum. Since the red blood cells contain an enormous store of potassium (from 410 to 440 mg per hundred cubic centimeters) it is evident that any hemolysis will liberate potassium into the serum. It was found that, when even the slightest trace of hemolysis could be noted, the potassium content of the serum was greatly increased—frequently to 30 and 60 mg per hundred cubic centimeters. Likewise, when the serum stands in contact with the clot for a considerable length of time, potassium diffuses out from the corpuscles. The rate of this diffusion is shown in the following experiment. Blood was drawn

<sup>8</sup> Clausen, S. W. J. Biol. Chem. 36: 479, 1918.

from a subject into a number of tubes, which were allowed to stand at room temperature for varying lengths of time before centrifuging and separating the serum from the clot. At varying intervals the serum was separated and samples analyzed for potassium. The results are given in Table 2. The concentration of potassium in the serum remains approximately unchanged for two hours, then mounts quite rapidly so that within twenty-four hours there is a marked increase, even though there is no hemolysis.

In one case of epidemic encephalitis, blood was taken by cardiac puncture fifteen minutes after death and the serum was separated immediately. The potassium was found to be increased to 45 mg. Meyers and Short have noted a similar increase after death in both blood serum and spinal fluid. Evidently some change occurs at death which allows a rapid diffusion of potassium from the cells.

After serum has once been separated from the corpuscles it can be kept for a considerable length of time without affecting the esti-

TABLE 3—*Potassium Values in Various Pathologic Conditions*

Serum No	Diagnosis	Potassium, Mg per 100 C c
1	Puerperal sepsis	19.2
2	Pyelitis	18.0
3	Pneumonia	17.7
4	Tonsillitis and cervical adenitis	23.0
5	Pneumonia	20.9
6	Scarlet fever	20.3
7	Subacute endocarditis	20.9
8	Pneumonia	18.1
9	Diabetes mellitus	20.2
10	Diabetes mellitus	19.9
11	Pernicious anemia	22.0
12	Pernicious anemia	21.7

mation of potassium. Even after standing for a month such serum gave reliable values for potassium by the method used in this investigation.

We have found, then, that the method of Kramer and Tisdall is reliable within an error of  $\pm 5$  per cent, as stated by the authors. To obtain, however, the true concentration of potassium as it exists *in vivo* precautions must be taken (1) to remove all the red blood cells by centrifuging the serum, (2) to prevent hemolysis, (3) to separate the serum from the clot within half an hour after the blood is drawn. Observing these precautions we have invariably found the potassium content of normal serums to be from 18 to 22 mg per hundred cubic centimeters.

#### POTASSIUM OF THE SERUM IN VARIOUS PATHOLOGIC CONDITIONS

Table 3 shows the values for potassium which we found in twelve persons suffering from various pathologic conditions. In all of these a normal content of potassium was found. In the two cases of per-

nicious anemia studied, there was evidence of marked hemolysis occurring within the body, as shown by the increase of bile pigments in the serum and of the urobilin in the urine. In spite of the fact that this destruction of red blood cells must liberate potassium, the concentration of this element in the serum was apparently maintained at the normal level

#### POTASSIUM OF THE SERUM IN NEPHRITIS

The possibility of potassium retention in nephritis has aroused considerable interest. Smillie<sup>9</sup> reported that one nephritic patient to whom

TABLE 4—*Potassium of the Serum in Nephritis*

Serum No	Patient and Age	Diagnosis	Date	Edema	Serum		Serum Potassium, Mg per 100 C c	Condition on Discharge
					Phthalic, per Cent	Nonprotein Nitrogen, Mg per 100 C c		
13	C S 5 yrs	Nephrosis	1/20/22 3/10/22	Very marked generalized	70		64 62 20.9 20.3	Unimproved
14	E McC. 2 yrs	Nephrosis	3/10/22	Very marked generalized			66 21.5	Unimproved
15	M G 9 yrs	Acute glomerulonephritis	1/20/22	None			80 22.0	Well
16	W S 7 yrs	Acute glomerulonephritis	6/28/21	Slight, face and ankles	45	25	23.5	Well
17	A F 20 yrs	Acute nephritis, bichlorid poisoning	11/ 8/21	Slight, face		100	25.1	Died
18	R P 21 yrs	Subacute nephritis	1/25/22 2/ 6/22	None	75 48	31 43	9.0 9.0 22.4 25.8	Worse
19	M P 16 yrs	Chronic nephritis (acute exacerbation)	11/25/22 2/ 6/22	Slight, face	39 50	34	8.2 7.4 19.2 18.7	Improved
20	G T 45 yrs	Chronic nephritis, hypertension	2/ 6/22	Slight, ankles	30	43	6.5 26.3	Unimproved
21	J D 47 yrs	Chronic nephritis, hypertension, myocardial insufficiency	1/25/22	None	47	27	8.4 21.3	Improved
22	P McC. 36 yrs	Chronic nephritis, hypertension, arteriosclerosis, myocardial insufficiency	2/ 6/22	Marked, legs	16	125	7.5 26.0	Died

10 gm potassium chlorid was administered showed marked toxic symptoms which he attributed to the potassium. Rabbits with uranium nephritis died with great suddenness following the ingestion of 1 gm potassium chlorid, while normal rabbits took from 3 to 4 gm without ill effect. He believed that this was due to the failure of the damaged kidneys to excrete potassium properly. Smillie did not determine the potassium content of the blood. His experiments, however, suggested that there might be an increase of the potassium in the blood of nephritics sufficient to account for some of the toxic symptoms. Meyers and Short found no increase in either the serum or whole blood of

<sup>9</sup> Smillie, W G. Arch Int Med 16 330 (Sept) 1915



seven patients with advanced nephritis showing marked nitrogen retention Loeb, Atchley and Palmer,<sup>10</sup> likewise, have found no increase in the serum potassium in nephritis with extensive ascites

In Table 4 we have recorded our findings in a number of different types of nephritis and nephrosis In most instances the potassium was found to be within the normal limits (from 18 to 22 mg ), but in four serums (Nos 17, 18, 20 and 22) there was a slight increase to 25 and 26 mg The two children with nephrosis (Nos 13 and 14) both had a very marked generalized edema and ascites but showed no increase of potassium in the serum Several of the patients with nephritis had slight edema, but we have had no opportunity to study any cases of so-called chronic parenchymatous nephritis with extensive anasarca Accordingly we cannot state whether this type of the disease might be associated with a more marked increase of potassium in the serum than we have found in any of our cases The four serums in which we did find a slightly increased amount of potassium were from patients with a definite nitrogenous retention and a diminished phenolsulphonephthalein excretion Two of these patients (Nos 17 and 22) died of uremia One patient (No 18) on January 25 had a phenolsulphonephthalein excretion of 75 per cent in two hours and a nonprotein nitrogen of 31 mg per hundred cubic centimeters of blood At this time the serum potassium was 22.4 mg The patient became clinically worse and on February 6 the phenolsulphonephthalein excretion had decreased to 45 per cent and the blood nitrogen had increased to 43 mg Coincident with these changes, the potassium of the serum had risen to 25.8 mg

Although these studies have shown that there may be this slight increase of the potassium of the serum in nephritis, we feel that the increase is so small that we are not justified, at the present time, in attributing toxic symptoms to it We have, on the contrary, been able to show that by the ingestion of potassium chlorid the potassium of the serum may be raised for a short period of time as high as 35 mg per hundred cubic centimeters without producing any marked toxic symptoms Of course, the retention of potassium in the tissues is not ruled out by our findings on the serum and still must be considered as a possible toxic factor in nephritis

#### POTASSIUM OF THE SERUM IN TETANY

The only other disease in which we have found the potassium content of the serum increased is tetany In four out of five cases studied, the potassium was moderately increased (from 23 to 29 mg ) These findings are the same as those of Kramer, Tisdall and Howland<sup>11</sup> As

<sup>10</sup> Loeb, Atchley and Palmer *J Gen Physiol* 4:591, 1922

<sup>11</sup> Kramer, Tisdall and Howland *Am J Dis Child* 22:431 (Nov) 1921

shown by a comparison of the figures for potassium and calcium given in Table 5 no definite relationship between the increase of potassium and the decrease of calcium could be made out

#### EFFECTS OF THE INGESTION OF POTASSIUM SALTS

We have attempted to determine to what extent the potassium of the serum may be increased by the ingestion of potassium salts. Two patients who had been receiving 1.3 gm potassium iodid three times a day for a long period of time were found to have 20.4 and 21.9 mg potassium, respectively, in 100 c.c. of serum. E. D. Osborne<sup>12</sup> has studied the effects on the blood serum of the administration of potassium and sodium iodids. He gave 1 gm, 5 gm and 20 gm of potassium iodid by mouth and noted that "this did not produce a corresponding rise in the potassium content of the blood serum, but,

TABLE 5—Potassium and Calcium Values in Tetany

Serum No	Age	Potassium, Mg per 100 C c	Calcium, Mg per 100 C c
23	7 months	29.0	5.7
24	3 years	18.9	4.6
25	6 months	27.0	7.2
26	5 months	23.7	5.1
27	7 months	23.1	6.0

TABLE 6—Results of Ingestion of Potassium Chlorid

Amount Taken	Potassium of the Serum, Mg per 100 C c			
	Before	1 Hour After	2 Hours After	3½ Hours
2 gm	20.6	20.4	25.4	
10 gm	20.6	24.6	29.8	22.9
15 gm	20.8		35.3	

on the contrary, a definite rise in the sodium content almost equal to that following (the administration of equivalent quantities of) sodium iodid. Following the 20 gm dose only a slight rise in the potassium content was noted." On the other hand, he found a marked rise of the iodin of the blood serum proteins after the administration of potassium iodid and only traces after the ingestion of sodium iodid.

We have made observations after the administration of the chlorid instead of the iodid of potassium. Unlike the iodid, the chlorid of potassium when taken by mouth causes a very marked increase of the potassium of the serum. The results of this experiment are shown in Table 6.

One of us (W) ingested 2 gm, 10 gm and 15 gm potassium chlorid in 300 c.c. of water on three different occasions. The potassium of the serum was found to be raised to 25.4, 29.8 and 35.3 mg per

hundred cubic centimeters after these respective amounts. The maximum increase occurred in about two hours, after which there was a rapid return to normal. The normal level was reached in about three and one half hours. No subjective symptoms were experienced beyond some nausea and sweating after the largest dose. Electrocardiograms were made during the experiment by other members of the staff. Certain changes in the curves believed to be characteristic were found and are being studied further.

#### SUMMARY

1 To obtain a correct estimation of the concentration of the potassium of serum as it exists in the body, precautions must be taken to prevent hemolysis and to separate the serum promptly from the corpuscles.

2 The potassium of normal human serum is fairly constant, varying only from 18 to 22 mg per hundred cubic centimeters.

3 The potassium content was within these limits in all pathologic conditions studied except nephritis and tetany.

4 In some cases of nephritis the potassium was increased to 25 and 26 mg per hundred cubic centimeters.

5 In tetany there is usually a slight increase of the potassium to from 23 to 29 mg. There is no definite relationship between this and the decrease in the calcium.

6 Patients receiving potassium iodid 13 gm, three times a day, showed no increase in the potassium content of their serum.

7 The ingestion of 2, 10 and 15 gm potassium chlorid raised the potassium of the serum to 25, 30 and 35 mg per hundred cubic centimeters, respectively. No subjective effects were felt but changes in the electrocardiogram were observed.

# SOME UNUSUAL DISTURBANCES OF THE MECHANISM OF THE HEART BEAT\*

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## I

### AN ECTOPIC TACHYCARDIA OF FIFTEEN MONTHS' DURATION

Attacks of simple paroxysmal tachycardia usually last but a few hours or at most a few days. Lewis<sup>1</sup> states that attacks which last a fortnight are rare and that longer attacks are unknown. D C Wilson<sup>2</sup> has recently reported an instance in which an attack of ten days' duration was followed by the development of gangrene of the forearm. This is the longest attack described in the recent literature. We were surprised, therefore, to encounter a patient with a tachycardia of this type that had persisted for approximately fifteen months.

**CASE 1—History**—Mr E K, an American student, aged 22, first seen by us in July, 1920. He complained of palpitation associated with rapid heart action. There was a history of whooping cough and measles in childhood, but none of rheumatic fever, chorea, scarlet fever or diphtheria. The patient had a severe attack of tonsillitis in 1918 and another in 1919. The tonsils were removed in December of the latter year. In February, 1919, he burned his hand, the wound became infected, and there was a local cellulitis for two or three weeks, followed by lymphangitis, which spread up the arm and involved the axillary glands. The infected glands were incised and drained, hot boric packs were applied, and the wound was irrigated with surgical solution of chlorinated soda (Dakin's solution). Gradual recovery followed. About April 10, 1919, two root abscesses were discovered, and the teeth concerned were removed under nitrous oxid anesthesia. After the first return of consciousness, "things turned black," and he relapsed for a short time into an unconscious state. During the following night, he was awakened by the rapid beating of his heart, amounting to distressing palpitation. He was kept in bed for three months, but rest had no effect on the heart rate.

When the patient first came to us, the tachycardia had been present continuously since its onset about fifteen months before. He was conscious of his heart beat at all times and was a little short of breath, but his symptoms were not sufficiently severe to interfere with his usual activities. He was attending the summer school at Washington University. He had found that if he took small doses of digitalis (15 drops of the tincture three times a day) and "behaved himself," the heart rhythm was regular, when he kept late hours, took excessive exercise or left off the digitalis for ten days or two weeks, the rhythm became irregular. He had also discovered that by holding the breath and straining (Valsalva experiment) he could suspend the tachycardia for a few seconds.

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\*From the Department of Internal Medicine, Washington University Medical School, and the Department of Internal Medicine, University of Michigan Medical School.

<sup>1</sup> Lewis, Thomas. *Clinical Disorders of the Heart Beat*, Ed 2, London, 1914.

<sup>2</sup> Wilson, D C. *Heart* 8 303 (Aug) 1921.

*Examination*—The apex beat was visible and palpable in the fifth interspace just outside the nipple line, the impulse was diffuse and poorly sustained. The heart rate was 164 per minute. There was a slight systolic thrill and a soft blowing systolic murmur at the mitral area. There was conspicuous pulsation in the veins of the neck and also in the left infraclavicular region. The cardiac dullness extended 3 cm to the right and 10.5 cm to the left of the midline in the fifth interspace. A teleoroentgenogram was made, the right border of the cardiac silhouette was 4 cm and the left border 8 cm from the midline. The patient was then asked to stop the tachycardia by the method described, and a second plate was made. The heart shadow was about 1 cm larger in all dimensions than on the first plate. This is the usual effect of the Valsalva experiment. The patient's exercise tolerance was excellent, and the remainder of the examination was negative.

Electrocardiograms showing the cardiac mechanism and the effect of holding the breath and straining at the time of the patient's first visit are shown in Figure 1. These records show that the disturbance of the heart beat responsible for the tachycardia was identical with that which gives rise to simple paroxysmal tachycardia. Holding the breath and straining brought about a sudden cessation of the rapid beating, but after from one to five seconds, it invariably returned as suddenly as it had stopped. Vagal pressure was without effect.

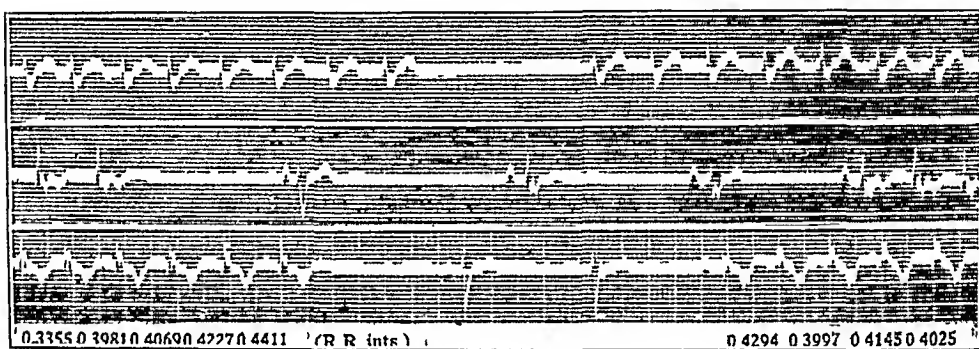


Fig 1 (Case 1)—Periods of bradycardia produced by holding the breath and straining. The decrease in heart rate preceding the cessation of the tachycardia may be noted. One time division equals 0.2 second.

When first examined, the patient was taking small doses of digitalis according to his usual custom. He was asked to discontinue it for two weeks in order to determine the nature of the irregularity that, so he stated, appeared when the drug was not taken. He complied with our request, but the irregularity failed to appear. The patient was then given digitalis in large doses, in the hope that it might produce partial heart block and thus reduce the ventricular rate. After taking 23 cc of the tincture in a period of seven days, he returned with a complaint that, whenever he rested, and particularly at night, the heart rhythm became irregular. Periods of bradycardia similar to those which he was able to produce by holding the breath and straining occurred spontaneously with great frequency. They were accompanied by weakness and dizziness, and fear of death. The drug also produced anorexia and nausea. He refused to take more digitalis. When he first arrived at the laboratory, the heart rhythm was regular, but after he had rested for an hour or more, the periods of spontaneous bradycardia suddenly returned. The records obtained are shown in Figure 2. No further observations were made.

*Comment*—So much for the essential features of the case, an unusual instance of very prolonged tachycardia of the simple paroxysmal type, with maintenance of surprisingly good cardiac function.

There are a few features of the electrocardiographic records which require brief comment. The ventricular complexes of the rapid rhythm are strikingly abnormal in form. They are diphasic, but of small amplitude, the Q-R-S interval is increased (0.1 second), and the Q-R-S group is curiously notched. That these complexes are of supraventricular origin is evident at once from Figure 2, in which complexes of the same form follow P deflections of normal outline. Their abnormal form must, therefore, be attributed to defective intraventricular conduction.

No auricular complexes can be identified during the rapid rhythm. In Leads II and III, the T deflection is curiously notched, and this notching may be due to the occurrence of an abnormal P deflection at this point. This view is supported by the absence of the notch from all complexes that follow normal P deflections except those that immediately precede the return of the tachycardia. This interpretation would, however, require the unwarranted assumption that the notch which deforms the final complex of each period of tachycardia represents a blocked auricular systole. A similar assumption would be necessary to explain the notching of certain idioventricular complexes that occur during the periods of bradycardia. Furthermore, we should be required to believe that the P-R interval of the first cycle of the returning tachycardia is much longer than the subsequent P-R intervals. In the face

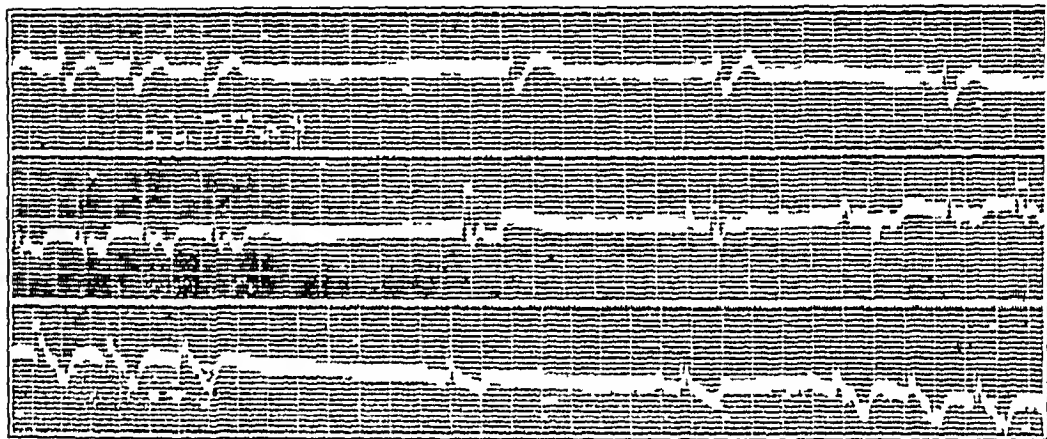


Fig 2 (Case 1)—Periods of bradycardia which occurred spontaneously after digitalization

of these difficulties, the auricular complexes cannot be located, and it is uncertain whether the tachycardia was of auricular or of atrioventricular origin.

In spite of the negative results of vagal pressure, the cessation of the tachycardia each time that the patient held the breath and strained must be attributed to vagus stimulation, and the spontaneous stops after digitalization undoubtedly had a similar origin. This effect of vagal stimulation is well known.

Many authorities advise against the administration of digitalis in cases of paroxysmal tachycardia. So far, we have not seen, in this disorder, high-grade heart block with consequent great reduction of the ventricular rate produced by it, but in several instances it has seemed that when digitalis was given the attacks were more easily controlled. We have also observed that drugs which produce a decrease in vagal tone, quinidin for instance, sometimes have the opposite effect.

The cessation of the tachycardia was invariably preceded by a conspicuous slowing of the ventricular rate. In this respect, the tachycardia differs from simple paroxysmal tachycardia, in which the end of the attack is not ordinarily preceded by slowing of the rate, whether the attack ends spontaneously or in response to vagal stimulation.

The cause of the bradycardia following the cessation of the rapid rhythm is not clear. It may have been the result of a continuation of the increased vagal tone, to which we have attributed the termination of the tachycardia, or it may be analogous to the bradycardia which follows the sudden production of A-V block. The idioventricular center, when suddenly called on to act as pacemaker, develops its rhythm slowly, and occasionally the sinus node, after it has been thrown out of action for a long period, seems to exhibit the same phenomenon (Lewis<sup>3</sup>)

The records show that, although the periods of bradycardia that were produced by respiratory experiments and those that occurred spontaneously after digitalization are similar, there is a distinct difference between them. The ventricular complexes which occur during the latter (Fig 2) are all of the same form as the complexes of the paroxysmal series, but the complexes which occur during the former are very variable in form, and many of them are of obscure origin (Fig 1). After digitalization, respiratory experiments produced a still greater variety of abnormal complexes. Occasionally, short stops were followed by resumption of the tachycardia without the occurrence of intervening nonparoxysmal beats (Fig 1).

## II

### TOXIC DEPRESSION OF THE CONDUCTIVITY OF THE PURKINJE SYSTEM

**CASE 2—History**—Miss E M B, aged 22, admitted to Barnes Hospital, Feb 26, 1920, complaining of persistent hiccup, vomiting and weakness, had left well until January 24, when she was seized with a severe headache and persistent anorexia. Two days later, she began to have pain in the upper abdomen. On the third day, she was nauseated, she vomited, and complained of pains in the ankles and feet. Her condition rapidly grew worse. One week before admission, her feet and legs began to swell. Three days later, she developed a persistent hiccup, and began to bleed from the nose and mouth, and to pass very small amounts of urine. She had had pain over the lower sternum and had been short of breath for some time, but lately these symptoms had become much worse.

**Examination**—The patient lay slightly propped up in bed, hiccuping, and groaning with pain in the abdomen and chest. She was slightly apathetic, and the mucous membrane of the mouth and tongue was so dry as to interfere with speech. There was dried blood about the nose and mouth and fresh blood in the nasal and oral secretions. The skin and mucous membranes were very pale. The respiratory movements were very deep, and the respiration rate was 16 per minute. Many rales were heard over the lungs, especially at the bases, and the breath sounds were harsh. The area of cardiac dulness was slightly enlarged. The maximum impulse was felt in the third interspace, 5 cm to the left of the midline. Less marked pulsation was felt in the fourth and fifth interspaces. On auscultation, a to-and-fro pericardial friction was heard over the central precordium and in the pulmonic area. The heart rate was 100 per minute, the rhythm was regular. The systolic blood pressure was 145, the diastolic, 95. There was ascites, with conspicuous edema of the ankles.

The blood examination revealed a high grade secondary anemia (1,900,000 red blood cells per cubic millimeter and 50 per cent hemoglobin) and a polymorphonuclear leukocytosis (32,000 white cells per cubic millimeter). The urine contained a large amount of albumin, and the tests for acetone and diacetic acid were both positive. In the sediment, many red blood cells, white blood cells, and granular, cellular, and hyaline casts were found. The blood contained 407 mg of nonprotein nitrogen per hundred cubic centimeters. The

3 Lewis, Thomas. *The Mechanism and Graphic Registration of the Heart Beat*, New York, Paul E Hoeber, 1920.

diagnosis was chronic nephritis, with secondary anemia, uremia and *pericarditis brightique*. There was probably a profound acidosis also, though no tests to determine the degree of acidosis were made.

The electrocardiogram taken on the day of admission to the hospital is shown in Figure 3. It is of the type commonly considered indicative of preponderant hypertrophy of the left ventricle. The Q-R-S interval is slightly increased, measuring approximately 0.12 second. The P-R interval measures about 0.20 second, the R-T interval about 0.36 second. T2 and T3 are unusually tall and pointed.

The electrocardiogram taken on the following day about three quarters of an hour before death is shown in Figure 4. So far as the direction and the amplitude of the individual deflections are concerned, it is very much like the first curve. The electrocardiographic intervals, however, are very dif-

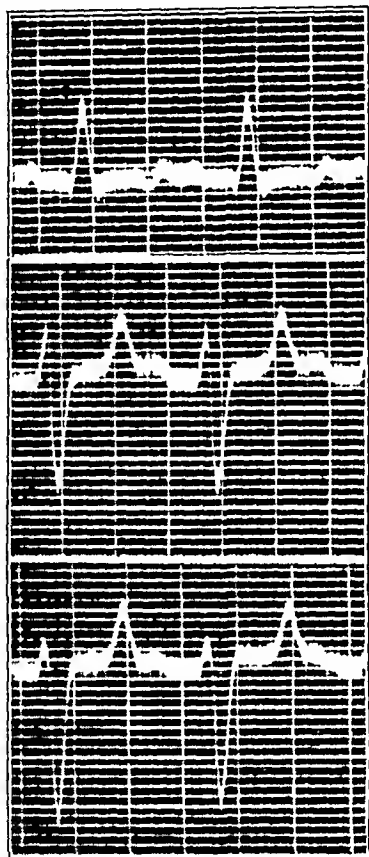


Figure 3

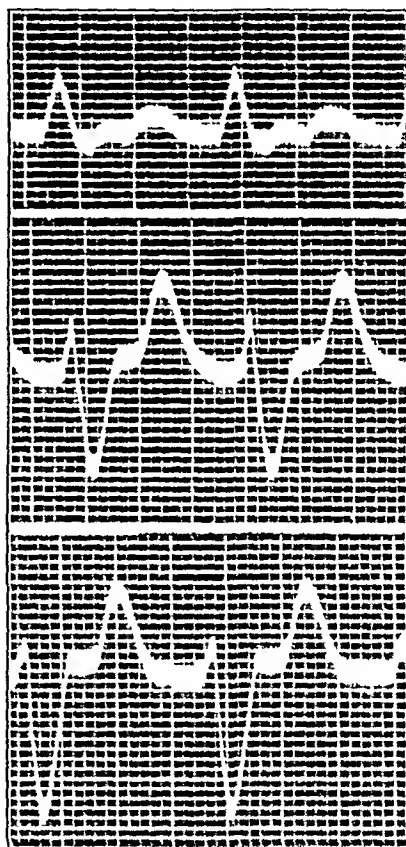


Figure 4

Fig 3 (Case 2) —Electrocardiogram taken on the day of admission to the hospital

Fig 4 (Case 2) —Electrocardiogram taken on the following day, one-half hour before death

ferent. The P-R interval cannot be determined because P is buried in the ventricular complex, but it is obviously greater than in Figure 3, the Q-R-S interval measures approximately 0.20 second and the R-T interval, about 0.56 second.

*Comment*—How shall these curves be interpreted? It is possible that the first electrocardiogram represents incomplete right bundle branch block, and that when the second curves were made, the block had become complete. This interpretation does not explain the change in the P-R interval. Another explanation may be suggested. It seems possible that the profound toxemia



from which the patient died may have led to a progressive, general depression of the conductivity of the specialized cardiac tissues. At the time the second electrocardiogram was taken, several ventricular extrasystoles were recorded (Figure 5). It will be noted that they show the same broadening that is so striking in the complexes of supraventricular origin. In bundle branch block, extrasystolic complexes do not ordinarily differ from those recorded in cases which show no evidence of defective intraventricular conduction. It seems, therefore, that the peculiar form of these extrasystolic ventricular complexes supports the idea that there was a toxic depression of the conductivity of the Purkinje system.

In this connection, we may remark that the form of the extrasystolic complex is not without importance in interpreting electrocardiographic abnormalities. It is true that ventricular extrasystoles give rise to complexes of widely variable form, but in most instances it is possible for one who has read many electrocardiograms to say whether a given extrasystolic complex differs widely from the usual types that occur. It seems to us hazardous to attribute curves of small amplitude or curves with long Q-R-S intervals to widespread lesions of the ventricular muscle of the ventricular conducting system when extrasystolic complexes of what might be termed "normal outline" occur in the same record. Widespread lesions must affect the extrasystolic complex as well as the supraventricular complexes, and although small changes

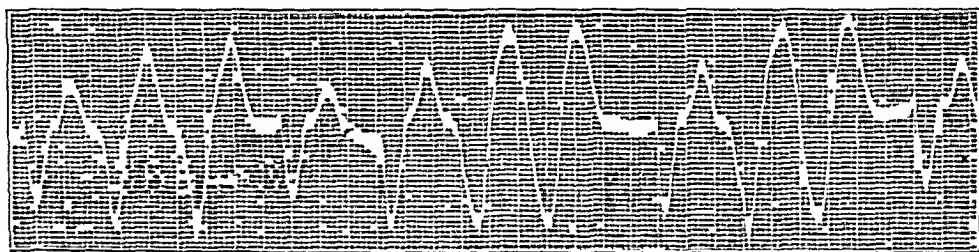


Fig 5 (Case 2)—Electrocardiogram taken immediately after that shown in Figure 5. The peculiar form of the extrasystolic complexes may be noted

in the former cannot be recognized, great changes may be, especially when they are of the same class as those exhibited by the complexes of supraventricular origin. We have seen several cases in which this has been possible.

### III

#### TRANSIENT COMPLETE BUNDLE BRANCH BLOCK

**CASE 3—History**—Mother L, a nun, was referred to the Washington University Heart Station for an electrocardiographic examination by Dr. Joseph Larimore, whose notes on the history and physical examination are given herewith.

In January, 1920, the patient complained of weakness and indefinite abdominal distress. The spleen and the liver were enlarged, and the white blood cell count was 27,000 per cubic millimeter, 85 per cent of the white cells were polymorphonuclear neutrophils. The examination was otherwise negative.

The patient gave a history of a bilious attack fifteen years before, of an acute arthritis of the right knee three years before and of many attacks of severe pain in the chest, believed to have been of cardiac origin, distributed over a period of three months, two years before. In August, 1919, she was "overcome by the heat." She had another attack of severe pain in the chest at this time. In September, an indolent ulcer appeared on the right great toe and persisted for more than a month.

**Operation**—A perinephritic abscess was suspected, and operation was advised. A posterior incision revealed a normal kidney. The peritoneal

cavity was then opened by an anterior incision, and the spleen, which was very large and so completely infarcted that practically no normal splenic tissue remained, was removed. The patient developed a right-sided pneumothorax following the operation, otherwise the postoperative period was uneventful.

*Course*—The nutrition and the general clinical condition improved gradually until March, 1920, when the patient began to be troubled by ascites. The abdomen was tapped three times at intervals of two weeks, on each occasion, about 80 ounces (2,400 cc) of a straw colored fluid of low specific gravity was removed. On each of the last two occasions, the left pleural cavity was also punctured and about 40 cc of fluid similar to that taken from the peritoneal cavity was obtained. After the third tapping, the patient began to have diarrhea, and this so favorably influenced the water balance that no more fluid accumulated in the serous cavities.

In May, there was an acute left axillary adenitis, associated with edema of the arm, which cleared up spontaneously after about one week. The patient had several attacks of acute gastro-enteritis. The Wassermann reaction and the complement fixation test for tuberculosis were both negative (August 3). Several blood examinations were made, all revealing a marked leukocytosis.

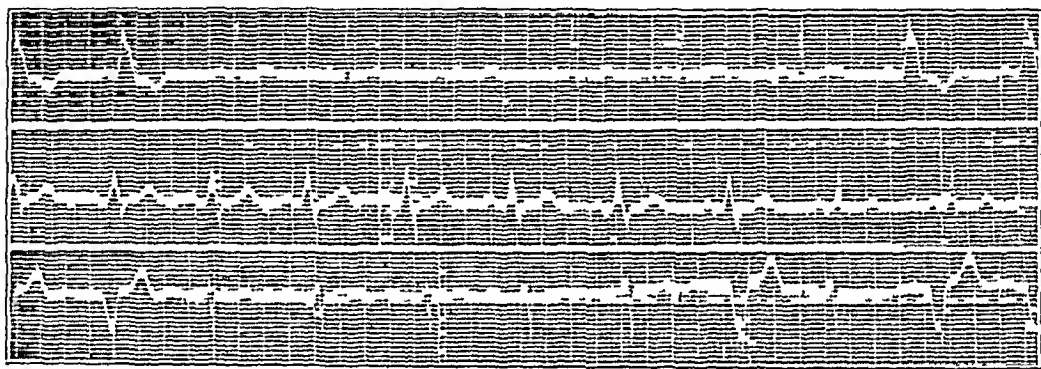


Fig 6 (Case 3)—Sudden transitions from bundle branch block complexes to complexes suggestive of left ventricular preponderance, and vice versa. These transitions were brought about by forced respiration. Several complexes which followed Cycle 5 (Lead III) were removed in order to shorten the bottom strip of record.

In February, 1921, the patient was greatly improved. She had been carrying on a large amount of administrative work and had no symptoms other than constipation, intense pruritis over the entire body, and slight edema of the ankles in the evening.

*Further Findings*—The temperature and the blood pressure were normal, and the lungs and pleurae clear. A soft systolic murmur was heard in the mitral area. There was no ascites. The liver edge was palpable 6 or 8 cm below the costal margin. The urine contained a trace of albumin and a few granular casts. The blood still showed a severe leukocytosis.

Two sets of electrocardiograms were made at this time. The first curves were characteristic of complete right bundle branch block. It was noted that, when the patient was asked to breathe deeply, a sudden change in the form of the electrocardiogram took place. Figure 6 shows that the bundle branch block complexes suddenly gave place to complexes suggestive of left ventricular preponderance. After a period of from a few seconds to a few minutes, the bundle branch block complexes invariably returned. All of the transitions took place suddenly.

At the time of the second examination, the patient was brought to the laboratory in a wheel chair (she had walked on the first occasion), and the

bundle branch block complexes were not present. They appeared, however, for a short time following mild exercise which consisted in from six to eight forward and sideward movements of the arms with a 5-pound dumbbell in each hand. As on the first occasion, all transitions from bundle branch block complexes to preponderance complexes took place suddenly, no transitional complexes were observed at any time.

*Comment*—The sudden onset of bundle branch block is analogous to the sudden onset of complete auriculoventricular block, an instance of which is described in this article. It differs in that it produces no symptoms and cannot be recognized without electrocardiographic records. In this instance, there was a relation between the appearance and the disappearance of the block and the variations in vagal tone produced by forced respiration and by exertion. In this respect, the case is similar to one reported by Wilson<sup>4</sup>. In that instance, however, complexes of transitional form occurred, and the onset of bundle branch block was accompanied by a shift in the location of the pacemaker.

#### IV

##### STOKES-ADAMS ATTACKS DUE TO THE SUDDEN ONSET OF COMPLETE BLOCK

*CASE 4—History*—Mr. T. H., an American coal miner, aged 39, was admitted to the University Hospital, April 4, 1922, complaining of pain in the right upper quadrant of the abdomen, shortness of breath and palpitation.

The patient gave a history of "inflammatory rheumatism" at the age of 18, in which the muscles of the legs were involved, but the joints were not red or swollen. He was ill for four or five weeks. No history of venereal disease was given, and the Wassermann test was negative.

The illness which brought the patient to the hospital began in September, 1921, with pain in the right upper quadrant of the abdomen. The pain was usually dull, but from time to time sharp stabbing pains were felt. The pain was not related to the taking of food and alkalis did not relieve it. It gradually grew worse, until in December he was forced to quit work. After five weeks in bed, he felt better, but when he tried to work the pain returned. He had never vomited. The pain was never precordial or substernal and it never radiated into the left arm. He had noticed some palpitation and shortness of breath since the onset of his illness.

*Examination*—Except for the cardiac abnormalities noted below, the physical examination was entirely negative. The apex beat was in the fifth interspace, 12.5 cm. from the midline. There was no increased dullness to the right of the sternum. There was a conspicuous systolic thrill at the aortic cartilage and in the suprasternal notch. Auscultation disclosed a rough aortic systolic murmur and a blowing aortic diastolic murmur. A mitral systolic murmur was also heard. The pulse showed no abnormalities, the radial artery was moderately sclerosed. The systolic blood pressure was 115, the diastolic, 105. Orthodiagraphic examination revealed a transversely placed, enlarged ventricular shadow, the aorta appeared to be lengthened and tortuous. The right border of the heart shadow measured 50 mm., the left border, 105 mm., from the midline. A roentgen-ray examination of the gastro-intestinal tract showed a twenty-four hour appendiceal shadow and abnormal irritability of the duodenal cap.

*Diagnosis*—The roentgenologist made a tentative diagnosis of duodenal ulcer or chronic appendicitis, but his findings were too vague to be conclusive. There was a slight secondary anemia. The urine was normal.

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4 Wilson, F. N. A Case in Which the Vagus Influenced the Form of the Ventricular Complex of the Electrocardiogram, *Arch. Int. Med.* 16:1008, 1915.

The provisional diagnosis was rheumatic heart disease with aortic insufficiency, and possibly aortic stenosis and slight cardiac weakness. The pain was believed to be the result of some intra-abdominal condition, probably duodenal ulcer, but the possibility that it was a cardiac pain of unusual distribution could not be ruled out.

*Clinical Course*—Shortly after the patient entered the hospital, he began to have attacks of Stokes-Adams syndrome of varying severity. In the milder attacks, the pulse disappeared for four or five seconds, the respirations deepened, the face became intensely flushed and consciousness was momentarily lost. In the longer attacks, the cyanosis and dyspnea were more conspicuous, and convulsions of a clonic type occurred. The patient often had fifteen or more attacks in as many minutes, and he had as many as thirty-four attacks in one day. Between April 6 and June 24, he had one or more attacks on thirty-six days and was free of attacks on forty-four days. He was often free of attacks for several days in succession (April 6-13, April 17-24, and May 15-29), and then had attacks daily for a similar period (April 25-29, April 30-May 5, June 6-12).

In view of the great irregularity with which the attacks occurred, it was difficult to determine the effect of various procedures on them. Epinephrin chlorid in doses of 15 minims of a 1:1,000 solution intramuscularly appeared to relieve the patient on a few occasions. May 4, he had several minor attacks at 3 p. m., epinephrin was given immediately, and at 3:30 p. m., the pulse rate was 68 per minute and the rhythm was regular. At 6 p. m., there was a recurrence of attacks, the heart rate was 36 per minute, and the pulse was weak and irregular. Epinephrin was given at once, at 6:05, the pulse rate was 40, at 6:10, 48, at 6:15, 60, and at 6:30, 72. It is questionable whether the change in pulse rate should be ascribed to the drug, since similar changes in pulse rate occurred with a disappearance of the attacks on other occasions, when no epinephrin was given. On several occasions, atropin sulphate in doses of one-fiftieth grain was given hypodermically, but it produced no obvious effect. From May 18 until June 24, barium chlorid in doses of one-half grain was given, three times daily by mouth. This drug was given on the advice of Dr. S. A. Levine, who pointed out to the authors that certain experimental work on barium indicated that it might enhance the idioventricular rate and possibly prevent ventricular standstill. In this instance, it had no effect on the frequency of the attacks.

During the patient's stay in the hospital, he had several attacks of severe abdominal pain, requiring morphin, and he suffered at intervals from less severe distress in the epigastrium that seemed to be relieved by antacids and an ulcer diet. The patient left the hospital, June 24, somewhat improved, but a follow-up report states that he died suddenly while at table, September 8.

When the patient entered the hospital, no facilities for taking graphic records were available. Early in June, an electrocardiographic outfit was installed, and records were made on several occasions. On two of these occasions, the patient was having attacks.

*Electrocardiographic Records*—The records made when the patient was free of attacks show a normal auriculoventricular sequence, with a slight prolongation of the P-R interval which measures 0.22 second (Fig. 7). The ventricular complexes are abnormal in form and show a decided prolongation of the Q-R-S interval, which measures 0.13 second.

June 10, a record was made while the patient was having severe attacks. It shows the end of one period of ventricular standstill and major part of another (Fig. 8). This record is tabulated below. Only R-R intervals are given except during the periods of ventricular standstill, when P-P intervals are given. In this as in those tabulations which follow, the letter R indicates that the corresponding ventricular complex occurs in response to an auricular stimulus, idioventricular beats which gave complexes of the



During the period of ventricular standstill, the auricular rate rapidly rises, this is usual,<sup>5</sup> and is probably the result of a decrease in vagal tone dependent on the fall in blood pressure

There can be no doubt that the ventricular standstill was brought about by the abrupt onset of complete heart block. As is well known the ventricular centers require a certain length of time to develop a rhythm, and consequently a period of ventricular standstill invariably results when the functional connection between auricles and ventricles is suddenly interrupted

June 23, other periods of ventricular standstill were recorded, the attacks at this time were of a milder type. The records obtained are tabulated below. Only R-R intervals are given

*Records Obtained June 23* 620, Ivc, 104, R, 048, R, 052, R, 048, R, 052, R, 052, R, 048, R, 052, R, 072, R, 072, R, 096, R, 088, R, 084, R, 096, R, 072, R<sup>p</sup> 156, Abc, 060, R<sup>p</sup> 164, Abc, 080, R, 064, R, 164, Abc, 084, R, 056, R, 064, R, 172, Abc, 116, R, 076, R, 084, R, 084, R, 092, R, and twenty-one other normal ventricular complexes

232, Ivc, 096, R, 052, R, 052, R, 052, R, 056, R, 064, R, 080, R, 088, R, 180, Abc, 468, R<sup>p</sup> 060, R, 056, R, 060, R, 092, R, 076, R, 464, Ivc, 104, R, 052, R<sup>p</sup> 084, R, 080

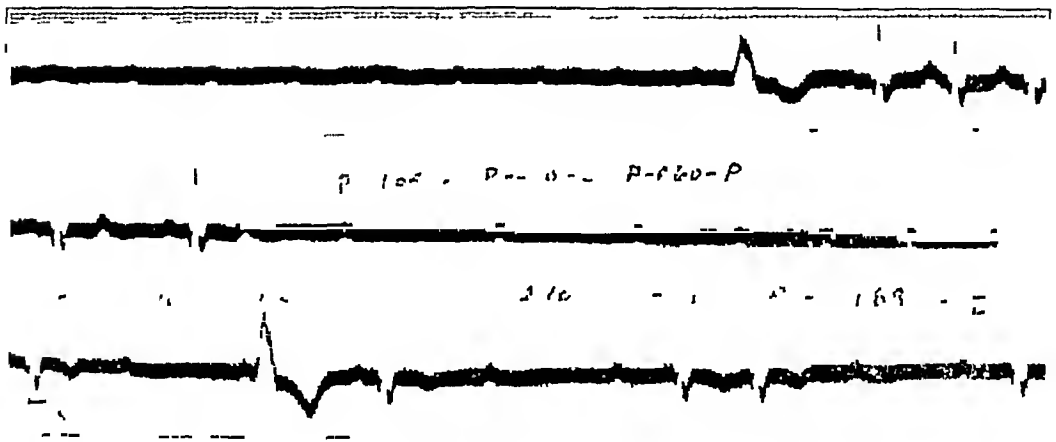


Fig 8 (Case 4)—Lead I top record The end of a period of ventricular standstill, middle record the beginning of a long period of ventricular standstill (taken, June 10, 1922), bottom record a period of very mild attacks (taken June 23)

R, 068, R, 072, R, 312, Abc, 168, Abc, 244, Ivc, 080, R, 064, R, 076, R, 320, Abc, 068, R, 068, R, 068, R, 084, R, 092, R, 240, Ivc, 220, Ivc, 216, Ivc, 092, R, 060, R, 072, R, 076, R, 232, Ivc, 216, Ivc, 052, R<sup>p</sup> 072, R, 068, R, 076, R, 088, R, 088, R, 232, Ivc, 216, Ivc, 208, Ivc, 096, R, 060, R, 072, R, 080, R, 176, Abc, 096, R, 216, Ivc, 056, R<sup>p</sup> 188, Ivc, 212, Ivc, 052, R<sup>p</sup> 068, R, 068, R, 076, R, 220, Ivc, 212, Ivc, 052, R<sup>p</sup> 070, R, 068, R, 084, R, 220, Ivc, 208, Ivc, 088, R, 072, R, 084

R, 072, R, 076, R, 080, R, 212, Ivc, 060, R (aberrant), 192, Ivc, 060, R, 080, R, 076

R, 080, R, 088, R, 204, Ivc, 084, R, 200, Ivc, 088, R, 196, Ivc, 200, Ivc, 076, R, 068, R, 072, R, 084, R, 208, Ivc, 180, Abc, 112, R, 064, R, 072

<sup>5</sup> Wilson, F N, and Robinson, G C Heart Block II Transient Complete Heart Block with Numerous Stokes-Adams Attacks, Arch Int Med 21 181 (Feb) 1918

*Comment*—The mild nature of the attacks at this time was due, first, to the irregular formation of impulses by one of the lower ventricular centers, and later to the development of an idioventricular rhythm, a center situated above the bifurcation of the His bundle acting as pacemaker. All of the longer periods of ventricular standstill occurred at the beginning of the period of observation. The natural period of the Ivc center appears to have been about 20 seconds, while that of the Abc center was about 16 to 18 seconds (Fig 8). The latter would probably have acted as pace-maker had it been able to produce impulses regularly. The irregular formation of impulses by some of the lower ventricular centers appears to be a common phenomenon when periods of ventricular standstill occur in rapid succession. It is possible that mechanical factors associated with the overdistension of the ventricles or with the auricular contractions may play a part in their initiation. These records suggest that there was a reciprocal relation between the severity of the attacks and their frequency. A number of attacks of ventricular standstill in close succession allowed the idioventricular rhythm to develop.

The cause of the sudden onset of complete block is not clear. A case identical with ours has been reported by Lewis,<sup>6</sup> in a somewhat similar case, Cohn, Holmes and Lewis<sup>7</sup> on histologic examination of the heart, found large blood sinuses in the A-V bundle. It seemed probable that transient engorgement of these sinuses might have led to the sudden attacks of heart block which were observed during life.

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<sup>6</sup> Lewis, T. Lectures on the Heart, New York, 1915.

<sup>7</sup> Cohn, A. E., Holmes, G. M., and Lewis, T. Heart 2: 241, 1909-1910.

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